I. OVERVIEW

A. Abciximab (ReoPro) is the **Fab** fragment of the **chimeric monoclonal** antibody **c7E3.** It binds with high **affinity** and specificity to the to **the** platelet glywprotein **(GpIIbIIIa)** receptor of human platelets and inhibits platelet aggregation. In animal models of arterial injury, 2 80% blockade of platelet GP **IIb/IIIa** receptors prevented arterial thrombosis. Clinical studies **have identified** dose regimens that **achieved** and sustained 80% blockade and inhibited platelet aggregation.

B. Clinical Settings

Platelets are thought to play a significant role in the initiation of arterial thrombosis. Initial investigations began with the agent in the setting of percutaneous **transluminal** coronary **angioplasty** (PICA). **The** use of PTCA is an **effective** means of enlarging the lumen of coronary vessels with atherosclerotic **narrowing. There** is, however, a risk of abrupt closure **of** the treated artery during or soon after the procedure in approximately 10 to 20 % **of** PTCA patients, which may result in ischemic cardiac complications, including acute **myocardial infarction** and death in some patients. Abciximab has been developed for use in patients uudegoing **PTCA as** an adjunct to **present** therapy for prevention of these ischemic complications.

C. EPIC trial results

Results of the EPIC (Evaluation of **c7E3** for the Prevention of Cardiac **Ischemic Complications) trial,** the pivotal **phase** III trial upon which approval of **c7E3 was based, showed:**

> (1) in 2,099 PTCA patients at high risk for abrupt **closure of** the treated coronary vessel, **c7E3** reduced the rate of primary events (a composite of acute MI, recurrent ischemia requiring urgent intervention, or death) at 30 days **from** 12.8% to 8.3% compared to placebo control. There was not a demonstrable benefit on mortality alone **(the** number of **deaths** was small, 12 each in the placebo and the bolus + infusion arms. Patients with unstable angina and patients at **risk** for acute **myocardial** Suction seemed to benefit the most **from** the use of **c7E3** during and after **PTCA.**
>
> (2) the frequency of major bleediig events was increased over placebo (10.6% vs **3.3%,** respectively were **the non-CABG** major bleeding rates in the bolus and infusion and placebo **arms,** respectively). Bleeding was **found** to be inversely **correlated** with **weight;** that is, **low-**weight patients bad **higher** rates of bleeding **(p<0.001).** All treatment groups received heparin in a standard, non-weight-adjusted regimen, suggesting weight-adjustment of the heparin dose might be an important variable. A single dose of **c7E3, consisting** of a **weight-**adjusted bolus and non-weight-adjusted **infusion, was** used in the trial.

Central issues in the discussions between the agency and **the** company during the licensing of **c7E3** involved the **examination** of **factors** which might reduce bleeding while not compromising **efficacy.** The **company** undertook to evaluate the **roles** of heparin dosage, weight adjustment of the heparin and **ReoPro** doses, and **features** of arterial sheath management in development of bleeding **complications.** A pilot trial, the PROLOG trial was **completed;** the **EPILOG** trial was the pivotal trial **which followed.**

D. Current Indication and Labelling

Abciximab (ReoPro) was licensed in December 1994 by the FDA for the adjunctive treatment of patients undergoing percutaneous coronary angioplasty (PTCA) who were at high risk for the development of abrupt closure of the treated artery and tbe development of subsequent cardiac ischemic complications. The regimen approved was that used in the EPIC trial, a weight adjusted bolus dose of 0.25 ug/kg administered 10 to 60 minutes prior to the start of tbe PTCA, followed by a fixed dose constant infusion of 10 ug/min for 12 hours. Abciximab was intended for use with concomitant a&coagulation; the regimens recommended were those used in the EPIC trial: aspirin 325 mg po within 2 hours of the procedure and daily thereafter, and heparin 10,000 to 12,000 units IV bolus prior to and boluses of to 3,000 units during PTCA to a maximum of 20,000 units. Heparin was continued for 12 hours following the procedure to maintain an a PTT of 1.5 to 2.5 times normal.

E. Results Of PROLOG Trial

This Phase II randomized trial of 103 patients evaluated adjustments in heparin dose and early or late removal of the femoral arterial sheath along with c7E3, which was given in a weight-adjusted bolus and non-weight-adjusted infusion for 12 hours from the start of PTCA, as was done in the EPIC trial. All patients received c7E3 plus either the "standard-dose" or "low-dose" heparin (approx 30% less; target PTT lower). The heparin adjustments are identical to those in EPILOG. "Early" sheath removal refers to removal within 6 hours of the PTCA; "late" removal refers to removal 18 hours after.

Results showed a similar primary endpoint rate in the standard and low-dose heparin groups, of 7.7% and 7.8%, respectively, (at 7 days) wmparable to that observed in the EPIC trial, 8.3% (at 30 days). Only 2 patients had major bleeding complications in the trial, but when a composite of major and minor bleeding, hematoma > 5 cm and transfusions was examined, late sheath removal and standard dose heparin were associated witb more bleeding.

F. Phase 4 Commitments

Objectives of the EPILOG trial included the phase 4 commitment to improve the risk to benefit comparison of the use of c7E3, and reduction of bleeding complications. Although not a phase 4 commitment sought by the Agency, the sponsor also hoped to broaden the labeling for c7E3 to include patients other than those at high risk of acute ischemic complications. They were advised to ensure that sufficient high-risk and low-risk patients would be enrolled to provide meaningful results for each subgroup by monitoring enrollment in the study.

Centocor also agreed to evaluate the success of platelet transfusions for patients referred for CABG after c7E3 and to evaluate the incidence of intracranial hemorrhage and stroke in a larger population by optimizing reporting in EPILOG.

IL EPILOG PROTOCOL

PROTOCOL TITLE: "A Phase III (IV) Randomized, Double-Blind, Placebo-Controlled Trial Evaluating 30-day and 6-month Clinical Outcome following Percutaneous Coronary Intervention in Patients Treated with c7E3 Fab Bolus Plus 12-hour Infusion Given with Either Standard-Dose Weight-Adjusted or Low-Dose Weight-Adjusted Heparin"

A. **Investigators/Trial Organization and Management**
The study was sponsored by Centocor, Inc., and managed jointly by the Cleveland Clinic Foundation and Duke University Medical Center. Principal Investigators were Harlan Weisman, M.D., of Centocor, Robert Califf, M.D., and Eric Topol, M.D., Chairman of the Cleveland Clinic Cardiovascular Coordinating Center, who along with Robert McCloskey, Centocor VP of Research, formed the Executive Committee,which was responsible for appointing a Safety and Efficacy Monitoring Committee to review interim data, and a Clinical Endpoint Committee to confirm cardiac and safety endpoint events, and for the final decisions on modifying or terminating the trial, based on the SEMC recommendation.

An Operations Committee supervised the conduct of the trial, and included Kate Cabot, MD and Harlan Weisman, MD (Centocor), and Drs Topol, Califf, and A. Michael Linwff (Cleveland Clinic). An investigator wmmittee including principal investigators from all study sites, met with the Operations Committee and served to make recommendations to the Executive Committee on trial related issues and publications.

B. Objectives
To evaluate the efficacy and safety of the combination of c7E3 bolus and infusion with either a standard-dose or a low-dose weight-adjusted heparin regimen in a broad population of patients (not limited to high-risk patients) undergoing percutaneous coronary intervention. The low dose heparin arm was included to test whether efficacy with ReoPro could be obtained with a reduced risk of bleeding by lessening the degree of heparin anticoagulation.

C. Trial Design
A Phase IV double-blind, placebo-controlled, randomized, parallel design trial was planned with 3 treatment arms, involving approximately 4800 patients at 80 US and Canadian centers.

D. Drug **Administration**
Patients undergoing percutaneous coronary intervention with an FDA-approved device were allocated randomly to one of three groups:

a) c7E3 Fab bolus and infusion plus "standard-dose" heparin (100 U/kg bolus to max 10,000 units for patients ≥ 100 kg), then Q 30 minute boluses or 10 U/kg/hr infusion adjusted to maintain ACT > 300 sec)

b) c7E3 Fab bolus and infusion plus "lowdose" heparin (70 U/kg bolus to max 7,000 units for patients 2 100 kg), then Q 30 minute boluses or 7 U/kg/hr infusion adjusted to maintain ACT > 200 sec)

c) placebo bolus and infusion plus "standard-dose" heparin (as above)

The bolus and infusion of c7E3 were weight-adjusted (0.25 mg/kg followed by 0.125 ug/kg/min to max 10 ug/min for patients *2 80 kg)* and *was the same* for *both* c7E3 treatment arms. *(Reviewer's Comment: The EPIC regimen used the same weight adjusted bolus but a fixed dose infusion of* 10 *ug/min).* The ReoPro infusion was continued for 12 hours; the heparin was to be discontinued immediately at the end of the index procedure, but was allowed to be wntinued (blinded) tbrough the 12 hour period, and then longer (open-label) if the investigator felt it was indicated.

(Reviewer's Comment: Heparin was actually discontinued after the index procedure in only 1,458 patients (53 % of the 2,752 with interventions attempted). The others had heparin continued for varying lengths of time, 90% for less than a total of 24 hours. This was balanced across treatment arms).

The study blind was maintained through the use of a 'heparin coordinator" at each study site who monitored the actual heparin dosing and ACT values. These were not known to the site investigators or individuals involved in patient care.

E. Concomitant Medications:

1. Heparin was recommended to be discontinued immediately upon completion of **the index** procedure but may have been continued longer at investigator **discretion;** open label heparin was allowed if indicated **after *the* 12** hour infusion was complete, to maintain the **aPTT** at 60 to 85 seconds

2. **Aspirin: 325 mg po within 2 hours prior to the procedure** and daily thereafter

3. Other cardiac medications: as per usual **practice (nitrates,** beta blockers, ACE inhibitors, etc.)

4. Arterial sheath removal and vascular access site care: it **was recommended that the** arterial sheath be removed within 4-6 hours of discontinuation of **heparin,** and in all cases when **the** ACT **was** c **175** or **PTT < 50;** it **could be left** in place **longer at investigator discretion**

F. Patient Population

The trial was intended to **enroll** "'all **comers"** with **coronary** artery **stenoses** 2 60 % who were thought to be candidates for a percutaneous **coronary** procedure, excluding patients with acute coronary syndromes; i.e. patients who fit the EPIC inclusion criteria with acute myocardial infarction or unstable angina. Patients with and without high-risk **morphologic** characteristics (as defined in the EPIC trial) were included.

Allowable procedures included balloon **angioplasty,** "bail-out" **STENT** placement (for failure of balloon procedure), and some types of atherectomy; **most** patients in **the** trial were treated with balloon **angioplasty**. Primary **STENT** placement was not initially included in the study; there was a **STENT substudy** added which randomized 123 patients to treatment with either **primary STENT** placement or **PTCA,** across the 3 treatment **arms** of the **EPILOG** study. (See ***Section* VIII of this review; the substudy** patients are included in the primary analyses of overall efficacy and safety for the EPILOG study.)

1. Inclusion: Patients > 18 years with a target artery stenosis greater than or equal to 60 % by visual estimation who are referred for elective or urgent **PTCA with an FDA-**approved device.

2. Exclusion: Unstable angina or acute MI by EPIC criteria in preceding 24 hours, Significant bleeding risks, unwntrolled hypertension, oral **anticoagulants, >** 50% stenosis LAD in absence of patent bypass **graft,** Rotational atherectomy, Planned Stent implantation (amended to include), PTCA in previous 3 months, allergic **risk factors.**

Reviewer's comment: EPIC includedpatients with acute unstable angina (n=826) and within I2 hours of onset of acute MI (n = 66) and high risk morphologic characteristics (n=1206). The benefit in prevention of cardiac ischemic complications was greatest in the patients with unstable angina and acute MI, who were at highest risk for the development of ischemic complications. EPILOG did not include either the patients with acute unstable angina or acute MI.

G. Efficacy Endpoints

1. Primary There were two co-primary endpoints.

(a) **Death, MI or urgent intervention:**

A composite of any one of the following within 30 days:

- all cause mortality,
- acute MI or reinfarction,
- seven ischemia leading to urgent repeat PTCA or CABG (urgent defined as within 24 hours of last episode of ischemia; severe ischemia defined as rest pain ≥ 5 min, or new ST-T wave changes, acute pulmonary edema or ventricular arrhythmiasor hemodynamicinstabilitypresumed ischemicin origin)

(b) Death, MI or repeat revascularization:

A composite of any one of the following within 6 months:

- **all cause mortality,**
- **acute MI or reinfarction,**
- repeat revascularization (any PTCA or CABG)

An overall comparison of the 3 arms using a logrank test was performed at both the 30 day and the 6 month timepoints. If significant, this was followed by pairwise comparisons of each ReoPro arm to placebo. Success was required on one of these primary endpoints (either the 30 day or the 6 month) compared to the placebo arm to demonstrate the efficacy of the treatment.

Reviewer Comment: The logrank test, a time-to-event analysis, was prespecified by the sponsor for the primary endpoint comparisons.. In the CBER analyses, the Fisher exact test statistic has also been computed on both the 30 day and 6 month primary endpoints to compare the incidence of endpoint events among treatment arms.

2. Secondary

(a) 6-month angiographic outcome (an angiographic substudy was to be done with 900 patients)

(b) Death, MI, or target vessel revascularization within 6 months (any vessel treated initially)

(c) Death, MI, or revascularization for clinically significant myocardial ischemia (unstable angina, recurrent stable angina or a positive functional test) within 6 months (includes urgent and repeat revascularizations for documented ischemia within 7 days of endpoint MI)

(d) Health economic analysis of cost-effectiveness of xx

Reviewer Comment: Analysis of efficacy by risk subset was prespecified in the analytic plan but not the protocol.

H. Safety Endpoints

1. Primary

(a) **Death and hemorrhagic stroke** incidence over the 6 month duration of the trial

(b) **Major bleeding events not associated with** CABG during hospitalization **or** within 7 days, whichever is earlier (by TIM study **criteria).**

2. Secondary

(a) **Nonhemorrhagic stroke,**
(b) Incidence of major bleeding in **c7E3** vs. placebo arms,
(c) Maximum decrease in Hemoglobin from **baseline,**
(d) Minor bleeding event incidence by **TIMI** criteria,
(e) Maximum Hemoglobin decline in **patients** ***having CABG*** during hospitalization,
(f) Incidence of serious adverse events thought related to bleeding,
(g) Incidence of bleeding requiring surgical intervention,
(h) Incidence of major bleeding by age and gender,
(i) Association of change in Hemoglobin with weight
(j) Maximum change in platelet count,
(k) Incidence of thrombocytopenia,
(l) Incidence and type of **transfusions,**
(m) Incidence of ***other adverse*** events.

I. Patient Enrollment

Patients wen **stratified** for randomization by the presence or absence of **high-risk** clinical and morphological characteristics in the artery to be treated. Any one of the **following combinations designated** a patient's status as high **risk:**

- Female, age ≥ 65 years, **and stenosis** with at least **1** Type B characteristic **(B1),**
- Diabetes **mellitus** and stenosis with at least **1** Type B characteristic **(B1)**
- Stenosis with 2 or **more** Type B characteristics **(B2),**
- Stenosis with 1 or more Type C **characteristics,** (C) or
- **Angioplasty** of an **infarct-related** lesion within 7 days following acute **MI** (documented by CK-MB elevation).

Lesion classification **is** based on the **ACC/AHA** classification scheme. Type A, B and C characteristics **are** based on assessments by **angiography** of vessel **tortuosity,** accessibility of lesion, presence or absence of thrombus, calcification, and other criteria. (See Appendix 1)

The protocol specified the expected enrollment of 40% high risk patients and 60% lower risk patients by this scheme. At randomization, the lesion assessment was based on the clinical history and a general **evaluation** (see Appendix 2) of whether Type B or C characteristics were present upon review of the **screening angiogram** by the investigator **(in** some cases, only films **from** a **referring** cardiologist were reviewed).

After the index procedure was performed, and in some cases after the patient's hospital discharge,a detailed description of lesion morphology was completed on the case report **form. On the CRF** details were recorded as to **the** nature and extent of calcification, presence or absence of thrombus, the length and **tortuosity** of the vessel segment, and accessibility of the **lesion. These details** provided a more complete assessment of the anatomic **features** of the vessels that were treated.

Reviewer Comment: The CRF was to have been completed based on the pre-procedure assessment of the patient's clinical and lesion morphology characteristics. However, the CRF was completed at anytime up to 3 weeks after the procedure, with knowledge of the outcome of the procedure, and in some cases, knowledge of the patient's subsequent clinical course, and may have been influenced by these factors.

J. Randomization was performed at the Duke University Coordinating Center. A 24-hour telephone hotline was used. When a site called to randomize a patient, responses to questions on inclusion and exclusion criteria were entered into a computer system that identified kit numbers available at the site and the kit to be dispensed. Centocor and participating physicians did not have access to the code. All randomization was done centrally, with stratification by risk status, study site and whether or not a patient was participating in the STENT substudy. Certain sites also enrolled patients in the Angiographic Substudy; all patients at those sites were enrolled in the substudy. The randomization code was created by the Duke University Medical Center Department of Clinical Epidemiology and Biostatistics.

K. Blinding Study agent vials were labeled at Centocor, and shipped to Duke. The Duke University Core Pharmacy performed blinding, numbering and assembly of treatment kits, and assignment of kits to sites. Core Pharmacists had access *only* to data liiing vials numbers to treatment assignment and vial numbers to study site, but did not have access to data linking vial numbers to patients. Unblinding could only be initiated by an investigator, in case of an emergency, for an individual patient, by cutting the label on the vial. The label was then placed in the patient's CRF, and the page forwarded to the data monitoring group to be kept in a locked cabinet until trial completion.

Heparin coordinators were assigned at each study site to maintain the blind to treatment arm assignment for members of the investigational team. Only the heparin coordinator at the study site knew the ACT and PTT values, and directed the changes in heparin dosage/ administration throughout the time of study agent administration. The heparin coordinator was not allowed to make study related observations other than recording the ACT measurements or heparin dosage adjustments. The CRF pages (15 and 16) with the heparin and ACT data were sequestered until trial completion. If blinded heparin was continued after the index intervention, the heparin coordinator was responsible for starting the infusion in the cath lab; later adjustments to the infusion rate were made on a volumetric basis by other individuals based on PTT only without knowledge of the actual dose being administered, as only the heparin *coordinator knew the* concentration.

HACA data was analyzed at Centocor. A separate recording and tracking system was used for these data to maintain the blind. All samples, through 6 months were to be shipped and run at the same time.

In some cases, open label use of commercial ReoPro was allowed at investigator discretion. In such cases, if prior to completion of study agent infusion, the investigator was to unblind the study agent to determine if a ReoPro bolus was needed, and note the date and time of discontinuation of study agent, These data were recorded on a separate CRF page and sequestered until trial completion.

L. Calendar of Assessments

The screening history and labs, including CBC, platelet count, PT, PTT, BUN, and creatinine were to be done within 7 days prior to randomization. Within 2 hours prior to randomization, another vital signs reading was taken, and CPK, CPK-MB, EKG, Hemoglobin, Hematocrit, BUN and creatinine.

Study drug was to he administered within 10 to 60 minutes prior to the start of the index procedure. Heparin and aspirin were initiated and continued per protocol. For patients who were pretreated with heparin prior to the start of study agent, this non-study heparin was to have been discontinued at least 5 minutes prior to the baseline ACT. Prior to each angiogram, the patient received 100 to 300 ucg of intracoronary nitroglycerine as a vasodilator.

A scout angiogram was typically performed prior to the procedure, and followed by the procedure itself, which took from twenty to sixty minutes (a smaller number of more technically difficult procedures were prolonged to up to ninety minutes).

Assessments after the procedure included vital signs q one hour x4, then q 6 hours x 4, timed from the bolus of study agent, EKGs on arrival to the ward and daily thereafter while hospitalized, at 30 days and at 6 months, platelet counts at 30 minutes, and at 2, 12, and 24 hours after the bolus, then daily until day 3. Platelet counts were obtained for any at discharge values < 150,000, at 30 days and 6 months. Any platelet counts of < 100,000 were repeated and verified in a citrated tube, and counts redetermined at 2 and 4 hours. Verified thrombocytopenia was followed with daily platelet counts until platelets returned to > 100,000 and within 25 % of the baseline value. For platelet counts below 60,000, heparin, aspirin, and study agent were to be discontinued. Transfusion of platelets was recommended if the platelet count dropped below 50,000.

Hemoglobin and hematocrit were done at 12 hours after the study agent bolus. Other laboratory assessments at 36 hours after bolus or prior to discharge included CBC, platelets, PTT, BUN and creatinine. For patients discharged more than 60 hours after the bolus, the same labs were to be repeated at 60 hours.

During the procedure, ACT was monitored as described elsewhere. The ACT or aPTT was to be obtained immediately prior to sheath removal, and the sheath was only to be removed when the ACT was c 175 or the PTT < 50. Patients who were to have study heparin continued after the procedure were to have a PTT at 6 hours after completion of the procedure for adjustment of the heparin infusion. Cardiac enzymes were obtained at 2 hours, then q 6 hours from study agent bolus through 24 hours, then q 8 hours for 48 hours or until discharge.

Post procedure angiograms were performed at the conclusion of the index procedure on all patients. The patients entered in the Angiographic Substudy were to undergo repeat coronary angiography at 6 months (184 to 275 days post randomization). The angiography was encouraged to be performed at the same institution, and catheter size and procedures specified.

Human anti-chimeric antibody (HACA) responses were evaluated at 7 days or discharge, 30 days, and 6 months following treatment for all patients in the angiographic substudy.

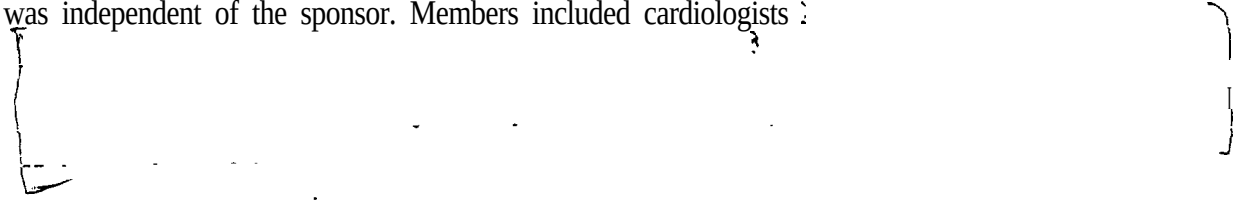
M. CRF and Field Monitoring

(1) the Medical Monitor Reviewer was _____ an attending cardiologist at - - - _____--- his duties included review of 30 day CRFs to identify possible adverse or endpoint events and clinical abnormalities or inconsistencies on the CRFs needing clarification.

(2) Field monitoring of CRFs and monitoring of sequestered heparin dosing and ACT data were performed by a CRO, the _____ An independent data management group, _____ --- was responsible for entry and query of the sequestered CRF data.

N. Interim Safety and Efficacy Monitoring

Interim data review was performed by an external Safety and Efficacy Monitoring Committee, which was independent of the sponsor. Members included cardiologists :



The Committee was to perform Interim Analyses after 1500 and 2500 patients had been enrolled. The primary endpoint was death or MI within 30 days, to ensure that the efficacy of the treatment was not reduced in the low dose heparin arm, resulting in higher numbers of cardiac events in those patients, Efficacy data were only available to the committee at the Interim Analysis, and not for continuous efficacy monitoring. Serious adverse events thought reasonably relatedto study agent were also monitored by the SEMC on au on-going basis.

SEMC recommendations to stop the trial were transmitted initially to Dr. McCloskey and 'Dr. Califf. Dr. McCloskey was to notify the FDA and then inform the full Executive Committee, which was responsible for determining whether to accept the recommendations. Written records of all communications were to be kept and held in escrow until the end of the trial.

The Biostatistics Department at the Cleveland Clinic had primary responsibility for interim data analyses and presentation to the SEMC. The Statistician was a n&voting member of the SEMC. Centocor was responsible for final data analyses after completion of the study.

0. Endpoint Assessment

1. A central Clinical Endpoint Committee reviewed CRFs, EKGs and other supporting data or clinical tests results (e.g. CT scan, CK values, Hb,.Hct, discharge summaries and operative notes) on all patients suspected of having all primary and some secondary 30 day and 6 month cardiac endpoint events, deaths, all strokes and major and minor bleeding events. Patients were flagged for CEC review with possible endpoint or bleeding events using computer screens. The CEC coordinator or one of 5 co-coordinators reviewed all cases that were not flagged for CEC review to determine if an endpoint may have occurred; any of concern were then forwarded to the CEC.

The role of the CEC was to confirm the occurrence of these *events.* CEC review was blinded to treatment group. Agreement of a minimum of 2 CEC reviewers was required to rule in an endpoint or event.The CEC at the Cleveland Clinic was composed of 23 cardiologists, 17 noninterventional cardiology fellows, and 6 noninterventional cardiology staff members. The CEC at Cleveland Clinic reviewed data on all patients from all other enrolling sites. A supplementary CEC was set up at Duke University Medical Center to review patients enrolled at the Cleveland Clinic. None of the CEC members were investigators in the trial.

A Cleveland Clinic neurologist, Cathy Sila, M.D.) reviewed and adjudicated all cases of suspected stroke. Dr. Sila was provided with CRF data and copies of contrast CT or MRI scans.

2. A central EKG Core laboratory reviewed all EKGs for the presence of Q waves. This blinded review identified patients with possible Q wave MI that may have been missed by other screening procedures. The CEC was informed of the EKG Core Lab's readings on cases it reviewed. EKG's at all timepoints were reviewed: baseline, 7 days or hospital discharge, 30 days, and 6 months.

3. The Angiographic Core Lab at the Cleveland Clinic Cardiovascular Coordinating Center reviewed all coronary angiograms for patients enrolled in the Angiographic Substudy. All patients at certain sites were enrolled in this substudy; these patients underwent repeat coronary angiograms at 6 months post randomization. The con lab independently assessed the extent of coronary disease, target vessel and lesion morphology, quantitative **luminal** dimensions, and results of the index procedure at the 6 month timepoint. **The** objective was to assess the effects of Abciximab on restenosis .

Assessment was blinded to treatment group. Two reviewers were to assess each case, and disagreements were to be resolved by the laboratory Medical Director. Some of the members were investigators, but they were not allowed to review data on their own patients. A total of 286 patients was enrolled in this substudy; it was planned for

P. Planned Statistical Analyses

1. Interim Analysis A planned Interim Analysis **was** performed at **1500** patients. **The** primary endpoint for the Interim Analysis was death and MI at 30 days; the **primary** reason for this interim **was** to be **sure** that the low dose **heparin arm** did not result in a higher rate of cardiac events (reduced efficacy).

Pairwise comparisons were made between each of the Abciximab arms and the placebo **arm.** Unequal stopping rules were invoked for the interim analysis; a stricter criterion was required to halt the trial for efficacy than for safety reasons. The trial was to be stopped for a **p=.025,** one-sided if an experimental arm had a higher rate of death or MI than placebo, **and** for a **p=.0005 if au** experimental arm appeared better than placebo. Descriptive statistics were **to** be used to analyze bleeding complications.

The protocol called for a **second** interim analysis **at** **patients at the discretion of the** SEMC, however the trial was halted after the analysis on the 1500 patients. The analytic plan called for the interim analysis primary endpoint of death and MI at 30 days to become the primary endpoint ***for*** the determination of efficacy at the final analysis, if the study was halted for **efficacy** at the interim analysis. In this event, the 3 part composites specified at 30 days and at 6 months would **become** secondary endpoints.

2. Final Analysis

An overall test for any significant **difference** among treatment arms was performed first at the final analysis. This was a generalized **logrank** test ----- , time from randomization to event recorded; patients censored who do not reach endpoints in observation period) and significance was required at a one-sided p value of **.0287** for any difference among treatment arms.

If the screening **test** was significant, **then pairwise** comparisons were **performed of** each of the **ReoPro arms** to the placebo arm, also **using** a **logrank** test. Significance was **required at a p < .05** (one-sided) on one of the primary efficacy endpoints. Both the 30 day and 6 month primary endpoints **were analyzed in this way.**

Q. Amendments to Protocol and Analytic Plan
Au amendment **specifying** the **planned** proportion of high **and low** risk patients to be enrolled was put in place before the trial commenced in February 1995. Minor protocol changes (laboratory monitoring) were made once the trial was underway. A **protocol** for the **Angiographic Substudy** was submitted prior to the enrollment of patients at those sites, shortly **after** the trial **began.** The protocol for the STENT **substudy** was put in **place** in **June,** 1995, **and** the substudy, at **17** sites, began enrolling patients for primary STENT placement in **August 1995.**

R Definitions
The following definitions were used in the **trial,** and are provided hen to aid the reader in understanding the terminology used:

1. ***Baseline disease-clinical*** diagnosis of **unstable** angina not fulfilling EPIC criteria includes:
   1) angina at rest within the previous month or
   2) new onset exertional angina of less than two months duration or
   3) severe or frequent (≥ 3 times/day) **exertional** angina or
   4) accelerated angina (exertional angina that is **more** frequent **or** pncipitated by less exertion).

2. Target vessel is any vessel to be treated during the index procedure.

3. Severe myocardial ischemia requiring urgent repeat intervention (the **30day primary** endpoint): One or mom episodes of rest pain, presumed ischemic in origin and lasting at **least** 5 minutes, which result in either urgent repeat PTCA or CABG surgery.
   a) **To** be considered urgent the repeat procedure must **be** initiated within 24 hours of the last episode of ischemia.
   b) In the absence of pain, the **following** were **sufficient** evidence **of** ischemia: new ST or T **wave** changes, acute pulmonary edema, or **ventricular** arrhythmias presumed ischemic in origin.

4. Repeat revascularization for clinically significant recurrent myocardial ischemia (the 6 month primary endpoint) :

Includes 1) Any repeat **revascularization** procedure **(PTCA** or CABG) performed for any of the following reasons:
   a) Unstable angina, defined as in 1. Above,
   b) Recurrent stable angina,
   c) Positive **functional** test **(ETT** showing **≥1** mm horizontal or downsloping ST depression at **80 msec** after the J point, or **Perfusion** or metabolic scintigraphy showing reversible **defect** on exercise or pharmacologic stress testing, **or ECHO** or **MUGA** showing reversible wall motion abnormalities during **stress** testing)
   2) Repeat **revascularization** within 7 days of endpoint MI
   3) Urgent revascularization for **severe** myocardial ischemia.

III. STUDY POPULATION

A. Study Dates and Enrollment

Enrollment ran from February 29, 1995 through December 14, 1995, wben the trial was terminated for efficacy at the recommendation of the SEMC.
The trial was discontinued after the 1500 patient interim analysis as the efficacy parameter exceeded the prespecified threshold for the ReoPro treated arms; there was evidence of both reduced bleeding and of improved efficacy in the ReoPro arm with low dose heparin. At that point the enrollment was 2792 and the final analysis was performed. The sponsor notes that the Interim Analysis serves as their primary analysis of efficacy and safety, however.

(Reviewer's Note: *SEMC records have been reviewed; it appears appropriate procedure was followed.)*

B. Baseline Characteristics

1. Demographics

The study arms were well balanced with respect to age, gender, height and weight and race. Approximately 70% of patients in the study welt male, with a median age of 60 years. Ninety percent were Caucasian, 6% Black, 2% Hispanic and less than 1% each of other races. (see Table 1 on next page for a listing of baseline patient characteristics in all treatment arms.)

2. Cardiac History

More than half of the patients enrolled had a history of unstable angina, and 50% had a history of MI, 18% had an acute MI within 7 days. Patients with acute coronary syndromes (acute Ml within 24 hours or active unstable angina at presentation) were excluded, however. (see Table 1). Only 1.6 % of patients had a history of congestive heart failure, and 2 % had a history of any type of previous cerebrovascular accident (only 3 patients had a prior hemorrhagic stroke). All these were well balanced among treatment groups.

3. Indication for the Index Procedure

Nearly half the patients enrolled were referred for the index procedure because of unstable angina; *20%* for recent MI *(reviewer's note: MI* may *have been within 7 days but not 24 hours; acute unstable angina was also* excluded). (See Table 1). A positive functional test was the primary indication in one quarter of patients. These percentages were similar across treatment arms.

4. Type of Intervention

Most patients enrolled (76.4 %) underwent balloon angioplasty only; 20 % of patients underwent other percutaneous procedures, including directional atherectomy (144), rotational atherectomy (15), Laser (14), TEC athenctomy (8), and 56 were randomized to coronary STENT placement., Another 326 patients underwent bailout STENT placement (124, 81 and 12 l-least in the ReoPro Low Dose Heparin arm). STENT results are presented separately elsewhere in this report. Three percent of the index interventions were urgent procedures. Among other interventions, thrombolytics were used in only 9 patients in the trial. (See table 1 on next page.)

Table 1 Selected Baseline Characteristics[1]

Characteristic	Placebo n= 935	Reo + Lo Hep n= 939	Reo + Std Hep n = 918
Demographics			
Male (%)	674 (71.8)	668 (71.4)	670 (73.0)
Median Age, yrs (range)	60 (29, 80)	60 (31, 87)	60 (31, 85)
Median Weight, kg (range)	83.6 (46, 156)	84 (45, 163)	84 (44, 164)
History			
MI within 7 days (%)	170 (18.1)	170 (18.2)	156 (17.0)
Diabetes (%)	224 (23.9)	212 (22.7)	202 (22.0)
Prior CABG or PTCA	362 (38.6)	339 (36.2)	342 (37.3)
Indication for Procedure			
Unstable Angina (%)	474 (50.5)	434 (46.4)	420 (45.8)
Recent MI (%)	189 (20.1)	200 (21.4)	190(20.7)
Chronic *Stable Angina*	56 (6.0)	61 (6.5)	53 (5.8)
Positive Functional Test	193 (20.6)	212 (22.7)	218 (23.7)
Intervention Type			
Balloon Angioplasty	889 (96.3)	886 (96.0)	873 (96.4)
Balloon only	705 (76.4)	751 (81.4)	702 (77.5)
Atherectomy	57 (6.1)	55 (6.3)	55 (6.1)
Urgent	33 (3.6)	24 (3.6)	34 2.8)

[1] Only selected categories are included in this table

5. Risk Classification

Patients were stratified at randomization by the presence or absence of high-risk clinical and morphological characteristics in the artery to be treated. The protocol specified a projected enrollment of 40% high risk patients and 60% lower risk patients by this scheme. At the time of randomization, 64.4% of patients were thought to have high risk characteristics (balanced across arms), and only 35.6 % of patients were thought to be lower risk.

When risk status was assessed using the completed CRFs, over half of the patients determined to be lower risk at randomization were shifted to the higher risk category. This shift was balanced across treatment groups, and in fact, some patients shifted from higher to the lower risk category, but far fewer. By the CRF data, then, only 19 % of the patients in the trial were in the lower risk category. (See Tables 2a and 2b).

Table 2a **Patients By Risk Classification** At **Time Of Randomization And By Risk Re-Classification Based On CRF Data**

	Placebo + Std Hep n=939	ReoPro + Lo Hep n=935	ReoPro + Std Hep n=918
As Randomized			
High Risk Patients			
n	602	602	590
%	64.1 %	64.4 %	64.3 %
Low Risk Patients			
n	337	333	328
%	35.9 %	35.6 %	35.7
Based on CRF			
High Risk Patients			
n	748	738	7
%	79.6 %	79.0 %	32
			79.8 %
Low Risk Patients			
n	176	186	175
%	18.8 %	19.9 %	19.0 %
Unable to Classify			
n	2	5	2
%	0.2 %	0.5 %	0.2 %

Table 2b shows the total numbers of patients in the trial by risk status assessment at randomization and at CRF classification.

Table 2b High and Low Risk Patients At Randomization and By CRF

	Low Risk at Randomization n = 998	High Risk at Randomization a = 1794
Low Risk by CRF n = 537	391 39 %	146 8%
High Risk by CRF n = 2218	598 60 %	1620 90%
Unknown by CRF n = 37	9 0.9 %	28 1.6 %

The largest change occurred in the group categorized as low risk at randomization, shifting to high risk by the CRF. The majority of the changes were due to morphologic characteristics of the lesion which were categorized differently by the investigator at the time of CRF completion (see table 3a). **There were 23** of these patients who changed due to **clinical history only** (diabetes or previous **MI** not recognized at the time of randomization).

Of those whose status changed due to lesion morphology reclassification, most were changed **from** Bl to **B2;** these patients were found to have an additional B characteristic in **the** treated lesion at **the** time of CRF completion (see table 3b **).** Changes **occurred** in all categories, however.

Table 3a Number of Patients Whose Risk Status Changed from Randomization to CRF Completion by Reason for Change in Risk Classification

Reason for Change	Low to High Risk (n = 598)	High to Low Risk (n = 146)
History of MI	14 (2.3 %)	6 (4.1 %)
History of Diabetes	9 (1.5 %)	1 (0.7 %)
Diabetes and Lesion Morphology	2 (0.3 %)	0
Lesion Morphology Only	573 (95.8 %)	139 (95.2 %)

Table 3b Number of patients by lesion morphologic change

Low to High Risk Morphologic change	Number of patients (%) n = 575	High to Low Risk Morphologic change	Number of patients (%) n = 139
B1 to B2	356 (61.9 %)	B1 to A	30 (20.5 %)
B1 to C	67 (11.7 %)	B2 to B1	63 (43.2 %)
A to B1	29 (5.0 %)	B2 to A	28 (19.2 %)
A to B2	81 (14.1 %)	C to B1	13 (8.9 %)
A to C	42 (7.3 %)	Cto A	5 (3.4 %)

The most common lesion characteristics causing a change in status appear to have been length, eccentricity, **accessibility,** angulation, and contour (these were also the most common of the 11 criteria that were rated as B2 or C for **all patients).** The investigators were to have evaluated the screening **angiograms** by these same criteria at the time of randomization-as at the time of CRF completion, but **the** individual characteristics were not required to be listed at **the** time of randomization. Only an overall assessment of the risk status based on lesion morphology **and clinical factors(A, B1** or B2, or C) was made at randomization. **The CRFs** were **usually completed after the procedure** had been completed, or in some cases, after hospital discharge, up to 3 weeks after the procedure.

Reviewer Comment: The recording of lesion characteristics on the CRF was to have been performed based on the ***pre-procedural assessment.*** The hindsight ***of the procedural outcome (or subsequent clinical events) may have permitted a more complete assessment of the specific lesion characteristics, or in fact, a more biased assessment toward higher risk classification. See Appendix*** **2 and 3,** ***for copies of the randomization*** profile ***and the CRF*** **page** ***on which this information was recorded.***

Reviewer's Note: The possibility that bias may have entered into the assessment of risk status at the time of randomization has been considered as well. The sponsor has stated that only one letter was sent to the investigators encouraging the enrollment of low risk patients. That was after the interim analysis, and after most of the patients in the study had already been enrolled The sponsor also stated that the percentages of low and high risk patients enrolled did not differ before and after the letter was sent. Copies of correspondence and investigator meeting agendas have confirmed all of these statements to be true.

B. Patient Disposition

1. Protocol Violations

A total of 48 patients (1.7 %) did not meet inclusion criteria The proportion was similar across all 3 treatment groups (15 in the placebo arm, 17 in the Abciximab Low Dose Heparin arm, and 17 in the Abciximab-Standard Dose Heparin arm). All patients were included in the primary and secondary analyses of results. Most common reasons for violations included a PTCA within the previous 3 months (10) and Prothrombin Time greater than 1.2 x control (17). Others included hypertension (6), planned STENT (4), occlusion < 60 % (3), and a scattering of other masons.

2. Treatment Received vs Randomized

The primary statistical analyses were all Intent-to Treat, and included all patients randomized. Of the total 2792 patients, 97.6% were actually treated with the study agent as randomized. A total of 67 patients, (2.4 % overall, balanced among arms) did not receive study agent at all. Table 4 presents the reasons patients were not treated. Administrative reasons (did not meet enrollment criteria, etc.) and the anticipated risk of bleeding were most frequent, followed by patients who did not have a target lesion with ≥ 60 % stenosis and patients who received alternate medical therapy. Four placebo patients and 1 ReoPro Low Dose Heparin patient underwent CABG following randomization and were not treated.

Table 4 Reasons Patients Were Not Treated (some patients had more than 1 reason given)

	Total n=74	Placebo n=32	ReoPro Std Dose n=20	ReoPro Lo Dose n=22
Risk of Bleeding	12	3	4	5
Occurrence of Bleeding	6	1	4	1
Other AE or Abnormal Lab	1	0	1	0
No target lesion ≥ 60%	7	4	1	2
Alternate medical rx	7	3	2	2
Rotational Atherectomy	4	1	1	2
Planned STENT	5	2	0	3
CABG	5	4	0	1
Consent Withdrawn	6	3	1	2
Administrative	18	8	6	4

Of the patients receiving study agent, 10.3 % did not receive the full dose (balanced among arms) and some of those patients, (a total of 4.6 % in the study) received neither the full dose nor the protocol specified rate of administration due to nursing error or miscalculation. The largest number of patients are shown in the "Administrative" category in all three treatment arms. Deviations from the total dose and from the protocol-specified rate were minor and resulted in only minor deviations from the protocol specified time of 12 hours of administration of the infusion. (See Table 5).

Reviewer's Note: The sponsor was asked for information on the amount of deviation from the planned dose in the cases attributed as "administrative" by treatment arm. Details were provided on the 32 patients in the Abciximab Standard Dose arm and on the 27 patients in the Abciximab Low Dose Heparin arm. Nearly all of the deviations of rate of administration were minor (1-2 cc/hr, resulting in administration times a bit shorter or longer than the protocol-specified 12 hours). Nine@ percent of these patients received > 90 % of the planned dose. The remaining patients all received > 73 % of the planned dose. These data appear to have had no significant impact on the study results.

Table 5 Reasons Patients Did Not Receive Full Dose (treated patients; some had more than 1 reason)

	Total n=2725	Placebo n=913	ReoPro Lo Dose n=915	ReoPro Std Dose n=897
Patients not receiving full dose[1]	280 10.3 %	100 11.0 %	82 9.0 %	98 10.9 %
Patients not receiving infusion at a constant rate*	125 4.6 %	51 5.6 %	31 3.4 %	43 3.8 %
Risk of Bleeding	8	2	4	2
Occurrence of Bleeding	52	10	16	26
Thrombocytopenia	5	0	1	4
Other AE or Abnormal Lab	28	8	8	12
No target lesion ≥ 60%	8	3	3	2
Alternate medical rx	13	8	2	3
Rotational Atherectomy	4	2	1	1
Planned STENT	29	16	4	9
Failed PTCA	62	21	22	19
CABG	28	12	4	12
Death	1	0	0	1
Administrative	%	37	27	32

- study agent was discontinued after treatment was begun
2 A subset of the total; the actual rate of study agent administration varied from the protocol specified rate.

3. Completeness of Follow Up

The 30 day endpoint assessment required ≥ 27 days followup. A total of 84 patients (3 %) in the trial had incomplete follow up at the time of the 30 day database lock and had not experienced an endpoint event. These were evenly distributed across treatment arms. (see Table 6).

Most cases of missing 30day data (64 of the 84) were due to early follow-up visits. Over half of these patients (45) had at least 20 days followup. The reasons for the early followup visits are unknown, as they were not recorded on the CRFs. Seventeen (17) patients of the remaining 20 were subsequently located by the time of the 6 month database lock, so that all but 3 patients had complete 30 day followup at that time.

All patients with early 30 day visits had complete 6 month followup. There were only 3 patients who were lost to followtip prior to 30 days who were also missing at 6 months. There were 12 patients (0.4 %) who did not have complete 6 month follow up (defined as followup < 165 days and no event prior to last followup).

Table 6 Patients With Incomplete Follow-Up[1]

	Placebo n = 939 n (%)	Reo + Lo Hep n = 935 n (%)	Reo + Std Hep n = 918 n (%)
< 27 days	30 (3.2)	30 (3.2)	24 (2.6)
< 165 days	3 (0.3)	3 (0.3)	6 (0.7)

1 at the time of the database locks at 30 days and 6 months

(Reviewer's Note: In response to an information request, the sponsor submitted a reanalysis of rhe 30 day primary endpoint results using the 6 month database (including the 17 patients not included in the 30 day database). The missing data do not have significant impact on the results.)

4. Heparin Administration and **ACT** Values

The protocol specified adjustment of the heparin infusion to maintain an ACT during the procedure of greater than 200 seconds, and of greater than 300 seconds in the standard dose heparin and the placebo arms. There was a difference of 46 seconds on median ACT values between the placebo and the Abciximab-low dose heparin arms, and a difference of 78 seconds between the Abciximab-low dose heparin and the Abciximab-standard dose heparin arms; the protocol appears to have been followed with regard to heparin dosing. The ACT values were a little higher in the Abciximab-standard dose heparin patients than in the placebo arm, which used heparin in the standard doses alone. In Table 7, "pre-device" refers to after the bolus and infusion of study drug and just prior to use of the balloon or other device during the procedure.

Table 7 ACT Values During Index Procedure

Patients With Intervention Attempted	Placebo n = 923	Reo + Lo Hep n = 923	Reo + Std Hep n = 906
ACT pre-device (sec)	329 (311, 358)*	283 (246, 324)*	361 (326, 402)*
Max during procedure (sec)	340 (320, 378)*	299 (263, 345)*	375 (343, 425)*

* Median, Interquartile range

The maximum ACT shows a similar difference, as well, in the median values and in the interquartile range, indicating that there were many in the ReoPro Standard Dose Heparin arm who had maximum ACTs above 400. All ACT values for the ReoPro low Dose Heparin arm were most often below 300 seconds, as the protocol had specified.

Reviewer Comment: The ACT values in the Abciximab-standard dose heparin arm were consistently a bit higher than those in the placebo-standard dose heparin arm, suggesting the higher ACT was more easily achieved in the presence of Abciximab.

5. Study Treatment Unblinding

Unblinding occurred in 167 patients total in the trial (6 %); a bit more often in the placebo arm than in either ReoPro arm. Most of these involved unblinding of ACT' values only.

Table 8 Unblinding Of Treatment

	Placebo n = 939	Reo + Lo Hep n = 935	Reo + Std Hep n = 918
Any Unblinding	75	40	52
Heparin Unblinding	9	6	10
Study Agent Unblinding	15	3	13
ACT Unblinding	69	36	45

Note: some patients may be listed more than once

Unblinding of study agent occurred in a total of 31 patients (1.1 %) in the trial, fewer in the ReoPro Lo Dose arm, but all numbers are small. Heparin was unblinded in 25 patients total. ACT was unblinded in 150 patients, Of the 150 patients who had ACT unblinded, only 28 also had study agent or study heparin unblinded. The most common reason for unblinding was the necessity for understanding the coagulation status of a patient to undergo CABG; followed by STENT placement, particularly in the Placebo and Reo Std Dose arms (then wen more patients going to CABG and receiving STENTS in these arms). There were 2 patients unblinded because of hemorrhagic stroke (one in each of the ReoPro arms) and 1 pericardial tamponade (in the Reo Std Dose arm).

6. Patients Who Did Not Have Index Intervention

A small number of patients enrolled did not have the index intervention performed (see Table 9) Lack of a significant lesion with > 60% stenosis was the most common reason, followed by CABG or alternate medical therapy and administrative' reasons. One patient in each of the ReoPro arms did not have the procedure because of bleeding.

Table 9 Patients Who Did Not Have Index Intervention (not a complete list)

	Placebo	Reo + Lo Hep	Reo + Std Hep
Patients not having intervention	16	12	12
No Significant Lesion	7	4	4
CABG or Other Medical Therapy	7	3	4
Bleeding	0	1	1
Other	2	4	4

7. Sites

Of ~ sites planned, 69 sites actually enrolled patients. There were 58 US sites, accounting for 2,681 patients, and 11 Canadian sites, accounting for the remaining 111 patients. A total of 18 sites enrolled more than 50 patients; of these, only one enrolled more than 200 (201); 5 sites enrolled between 123 and 176 patients, 12 sites enrolled 50-100 patients and 27 sites enrolled between 20 and 50 patients. The remaining 22 sites each enrolled between 1 and 18 patients. There were 29 academic sites enrolling a total of 814 patients and 39 non-academic sites enrolling 1,977 patients.

IV. **EFFICACY** RESULTS -- PRESPECIFIED ANALYSES

A. Primary Endpoints

(Reviewer's note: primary prespecified analyses only included the overall composite rates; ***rates by component are also presented here for continuity)***

1. 30-Day Primary Endpoint composite and by component

The 30 day primary endpoint was a composite of all cause mortality, myocardial infarction (MI), and urgent repeat revascularizations for severe myocardial ischemia occurring during the 30 days post randomization. The overall test for any significant difference among the three treatment arms had a p value of < .0001. Pairwise comparisons showed a significant treatment effect in both the ReoPro arms on the composite primary endpoint compared to placebo; the composite endpoint occurred in 11.7 % of placebo patients and in 5.2 and 5.4 % of ReoPro treated patients, in the Low Dose and Standard Dose Heparin arms, respectively. The largest effects of ReoPro over placebo were seen in the occurrence of MI's and of urgent revascularizations. There was no significant difference in mortality between the arms, although there were a lower total number of deaths in the ReoPro treated patients.

Table 10 (see next page) presents the number and percentage of primary endpoint events by treatment arm for the composite and by component.

Figure 1 (see following page) presents the Kaplan Meier curves for the time to event data on the primary composite endpoint.

Table 10 All Randomized Patients 30 Day Primary Endpoint[1]

		Placebo n=939	ReoPro + Lo Hep n=935	ReoPro + Std Hep n=918
Death, MI, or Urgent Revascularization	n % 95 % CI p value[2] p value[4]	109 11.6 % (9.56 - 13.66)	48 5.1 % (3.72 - 6.55) < .0001 < .0001	49 5.3 % (3.88 - 6.79) < .0001 < .0001
Death	n % 95 %CI[3] p value[2] p value[4]	7 0.8 % (0.20 - 1.30)	3 0.3 % (-0.04 - 0.68) .1 .3	4 0.4 % (0.01 - 0.86) .2 .5
MI	n % 95 % CI[3] p value[2] p value[4]	81 8.7 % (6.83 - 10.42)	34 3.7 % (2.44 - 4.84) < .001 < .0001	35 3.8 % (2.57 - 5.05) < .001 < .0001
Urgent Revascularization	n % 95 % CI[3] p value2 p value[4]	48 5.2 % (3.70 - 6.52)	15 1.6 % (0.80 - 2.41) < .001 < .0001	21 2.3 % (1.32 - 3.25) < .001 = .0013

1 For the log rank test on the composite, patients were counted only once by most severe component. For the analysis by component, patients may have been counted more than once. All events were counted; patients who had more than one event are listed once for each event.

2 1 sided p values calculated for time-to-event analysis using Logrank test, sig < .05, comparison to placebo

3 95 % CI as per CBER Biostatistics review

4 2 sided p value calculated using Fisher's exact test, per CBER Biostatistics review

Figure 1 Kaplan-Meier Curve For 30 Day Time To Event Data

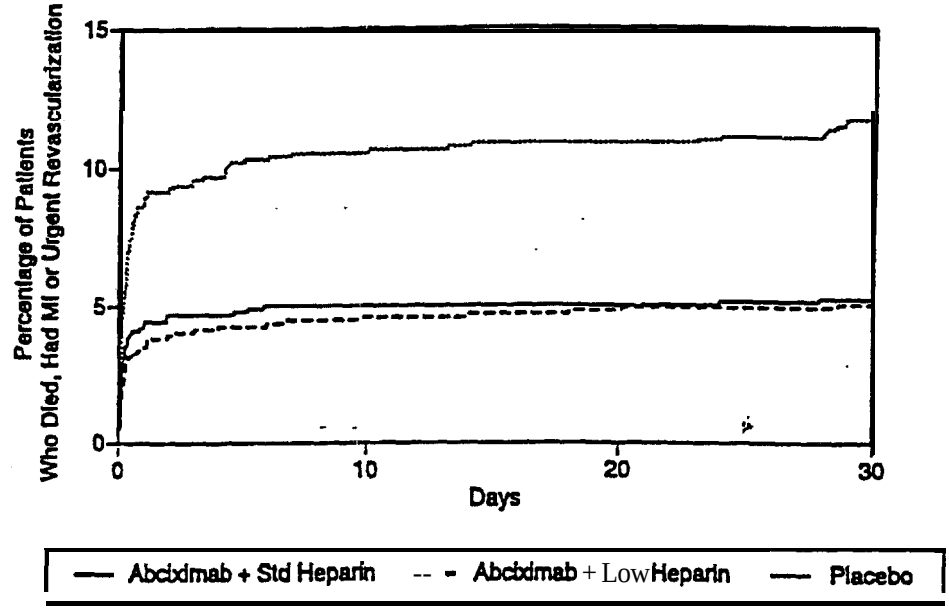


Figure 3 Kaplan-Meier Event Rates for Death, MI or Urgent Revascularization Through 30 Days in Randomized Patients (individual abciximab treatment groups are shown).

2. 6 Month Primary Endpoint composite and by component

The p value for the overall comparison is .015; it was required to be < .0287. Pairwise comparisons were then performed on each Abciximah treatment arm compared to placebo. A small advantage was seen for the ReoPro treated patients. The difference on this composite endpoint is statistically significant by the sponsor's analysis, but is less so than that seen on the 30 day primary endpoint. When the Fisher exact test is used, there is no statistical significance seen between the ReoPro arms and the placebo arm on this endpoint. (See table 11).

MI at 6 months is significantly reduced in the ReoPro arms, by both logrank and Fishers methods. and there is a trend to reduced deaths though the numbers are small and it does not reach statistical significance.

There was no significant difference in all repeat revascularization procedures among treatment arms at the 6 month endpoint. Pates for all revascularization catch up in the ReoPro arms to placebo rates by 6 months. This was due largely to similar rates for revascularization procedures that were not urgent among the treatment arms. There was still a trend toward improved rates of urgent revascularizations (see Table 28 in Section VB of this review).

Table 11 6 Month Primary Endpoint Composite and by component [1]

Patients		Placebo n=939	ReoPro + Lo Hep n=935	ReoPro + Std Hep n=918
Death, MI, or Repeat Revascularization	n % 95 % CI [2] p value [3] P value [4]	241 25.8 % (22.87 - 28.46)	212 22.8% (20.00 - 25.35) .034 .13	203 22.3% (19.43 - 24.80) .020 .08
Death	n % 95 %CI [2] p value [3] P value [4]	16 1.7 % (0.88 - 2.53)	10 1.1 % (0.41 - 1.72) 0.119 .32	13 1.4 % (0.65 - 2.18) 0.311 .71
MI	n % 95 %CI [2] p value [3] P value [4]	93 9.9 % (7.99 - 11.81)	47 5.0 % (3.63 - 6.43) < .001 < .0001	48 5.3 % (3.79 - 6.67) < .001 = .0002
Repeat Revascularization	n % 95 %CI [2] p value [3] P value [4]	180 19.4 % (17.56 - 22.69)	176 19 % (16.83 - 21.89) 0.354 0.68	167 18.4 % (16.11 - 21.15) 0.260 0.45

1 For the composite, Patients were counted only once by most severe component For the analysis by component, patients may have been counted more than once. *All* events *were* counted; patients *who* had more than one event are listed once for each event.

2 95 % CI as per CBER Biostatistics review

3 1 sided p values calculated for time-to-event analysis using Logrank test, sig < .05, comparison to placebo, per sponsor's analysis

4 P value, calculated using Fisher's exact test, per CBER Biostatistics review

Reviewer's Note: The 6 month primary endpoint includes all revascularization procedures, and the 30 day primary endpoint includes only those that fit the definition of urgent. There is a clear cut benefit in urgent revascularizations seen in the ReoPro arms at 6 months, although there is not an appreciable difference in total procedures. See Section VB of this review for further comment.

B. SECONDARY EFFICACY ENDPOINTS

1. Death, MI or target vessel revasculrrization within 6 months

There was no significant difference in total repeat procedures on the target vessel among treatment **arms at 6** months. The target vessel is defined **as** any vessel treated that was treated during **the index** procedure; includes urgent and non-urgent **procedures within 6 months followup.**

Table 12 Death, MI or target vessel revascularization within 6 months

Patients w events	Placebo n=939	ReoPro + Lo Hep n=939	ReoPro + Std Hep n=918
n	168	157	147
%	18.1 %	17.0 %	16.2 %
p value		.206	.117

* Logrank test sig < .05

2. Death, MI, or revascularization for clinically significant recurrent myocardial ischemia at 6 months

A significant difference is *seen* on this endpoint in the **ReoPro arms** compared to placebo (see Table 13 below). This endpoint is similar to the **primary 30-day** endpoint, although not identical. **This** endpoint includes urgent **revascularizations** for documented ischemia and repeat revascularization procedures after endpoint MI. This endpoint requires documentation of myocardial **ischemia, and** includes largely urgent procedures, but does not **require** that the iscbemia be severe, as does **the** 30 day primary endpoint.

Table 13 Death, MI, or Revascularization for Clinically Significant Recurrent Myocardial Ischemia at 6 **months**

Patients w events	Placebo n=939	ReoPro + Lo Hep n=939	ReoPro + Std Hep n=918
n	138	78	76
%	14.7 %	8.4 %	8.3 %
p value		<.0001	<.0001

* Logrank test sig < .05

*Reviewer's Note: An information request was sent to the sponsor regarding the **lack** of success in showing a **difference** in total revascularization procedures at 6 months. **The** sponsor's interpretation is that the **effects** of **ReoPro** on thrombus formation are significant enough to reduce the urgent revascularizations, even out to **6** months, but that the use of the product at the time of **PTCA** does not retard the progressive atherosclerosis in the coronary vessels, nor does **it** appear to affect the incidence of restenosis.*

3. Anglographic Outcome at 6 months
These data have been submitted separately in a substudy report by the sponsor and are reviewed in another document.

4. Health **Economic Analysis and Cost-Effectiveness of Treatment**
This was the subject of another substudy; those data are not being submitted with this application.

V. EFFICACY RESULTS – SECONDARY AND SUBGROUP ANALYSES

A. Primary Endpoints

1. 30 Day Primary Endpoint

a. Treated Patients
There was little difference between this analysis and the primary efficacy (Intent to Treat) analysis. Only 2.4 % of patients were not treated overall, and the proportion was similar across treatment groups.

b. By Risk Classification
Risk was assessed twice in this study, at the time of randomization, and following the index procedure when the detailed lesion morphology classification was completed. This study sought to extend the demonstration of efficacy seen in the EPIC trial to include patients at lower risk for acute cardiac ischemic complications following the procedure. Subset analyses by risk classification were not explicitly planned in the protocol, however.- The subset analyses show efficacy associated with Abciximab in the higher risk subset of patients, whether classified by the at-randomization or the CRF assessment. The low-risk subset as identified at randomization shows efficacy of Abciximab. The low risk subset as identified by the CRF assessment shows no trends toward efficacy (Table 14).

There was a small number of patients (25) whose clinical status was recorded incorrectly at randomization, and was corrected on the CRFs, resulted in reclassification of those patients by risk status. Table 15 (see next page) shows the primary endpoint event rates by the as randomized risk status, incorporating the changed risk status of the 25 patients whose status changed for clinical reasons. There is no substantial alteration in event rates by treatment arm when these changes are incorporated.

Table 14 Primary Endpoint Events At 30 Days By Randomized And By CRF Risk Classification

	Placebo n=939	ReoPro Lo Hep n=935	ReoPro Std Hep n=918
RANDOMIZED CLASSIFICATION			
High Risk Patients	602	602	590
Events	138	40	33
%		6.6 %	5.6 %
p value[1]		< .001	< .001
Low Risk Patients	337	333	328
Events	31	8	16
%	9.2 %	2.4 %	4.9 %
pvalue[1]	. .	< .001	< .001
PERCRF CLASSIFICATION			
High Risk Patients	748	738	732
Events	100	39	40
%	13.4 %	5.3 %	5.5 %
p value[1]		< .001	< .001
Low Risk Patients	176	186	175
Events	8	3	9
%	4.6 %	3.2 %	5.1 %
p value[1]		NS	NS

Source: Datasets

1 p value computed using Chi Square test as per CBER Biostatistics Review

Table 15 Primary 30 Day Endpoint by Randomized Risk Status after patients whose risk status changed for clinical reasons were incorporated

Patients with Death, MI or Urgent Revascularization	Placebo n=939	ReoPro Lo Hep n=935	ReoPro Std Hep n=918
High Risk Patients	611 78 12.8 %	609 40 6.6 %	599 33 5.5 %
Low Risk Patients	328 31 9.5 %	326 8 2.5 %	319 16 5.0 %

e. By Component by **Subgroup**

(i) **Age, gender and weight**
Men less than 65 years were the largest subgroup in the trial, and substantial reductions in the primary 30day endpoint **is seen in this group (see** Figure 2 below; hazard ratios are shown comparing **the placebo arm to the combined** Abciximab arms). Substantial reductions are also seen in women **<** 65 years, but then were fewer patients in this subgroup. For patients over age 65, there is a **trend** toward reduction of events that is of lesser magnitude in women, and is not statistically significant in either women or men. Again, there were far fewer patients in these subgroups.

The ReoPro bolus and the **heparin** bolus and infusions were weight-adjusted in this trial. Analysis of subgroups by body weight **<** 75 kg, 75 - 90 kg, and **> 90** kg shows a consistent reduction in primary endpoint events in all these groups, as is shown in Figure 2.

Of interest, the largest subgroup in the trial included patients weighing 2 90 kg. The Abciximab infusion was not weight adjusted for patients weighing over 80 kg. The improved primary endpoint **rates** in the **ReoPro** groups were seen consistently across patients weighing 2 80 kg also.

Figure 2 **Hazard Ratios for Primary 30 Day Endpoint by Age, Gender, and Body Weight**

Death, MI or Urgent **Revascularization** through 30 Days
by Body Weight, Age and Gender

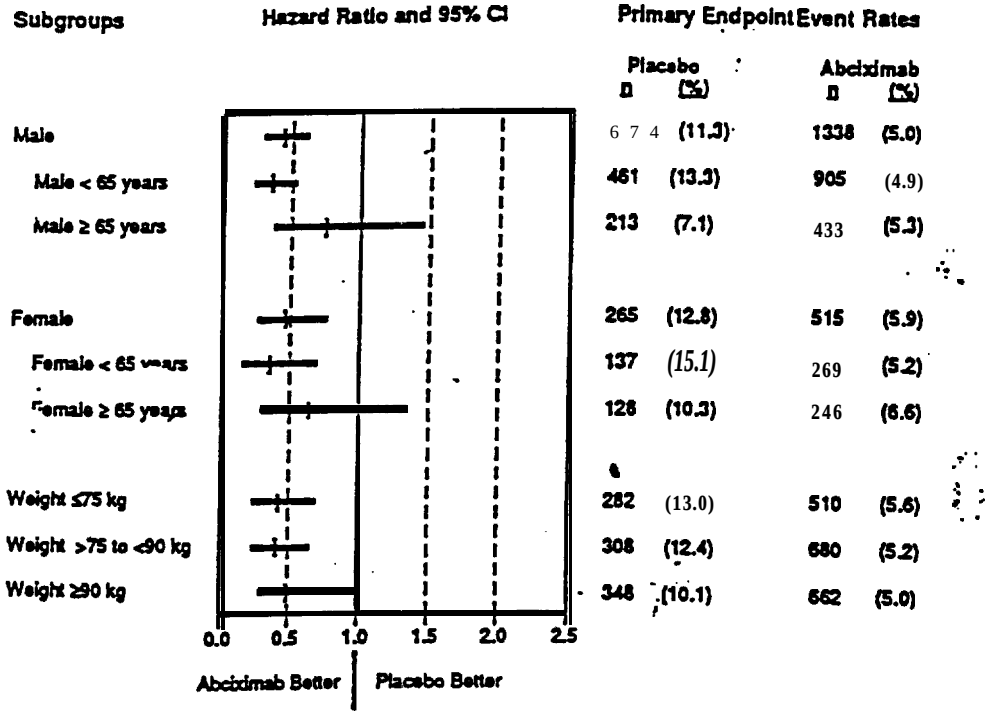


Figure 2 Hazard Ratios and the 95% Confidence Intervals (CI) for Death, MI or Urgent Revascularization by Gender, Age and Body Weight. The number of patients and the event rates are shown on the right side for each clinical event according to treatment group. Hazard ratios <1 indicate abciximab is better and hazard ratios >1 indicate that placebo is better.

[ii) History of Diabetes and prior Myocardial Infarction

The presence of **diabetes** and recent **myocardial infarction** in a patient's history may be factors which significantly **predict** risk of **ischemic** events. Patients with a history of diabetes **mellitus** comprised 22% of the patients in the study. **Primary** endpoint rates appear **significantly reduced in** both patients with and without a prior history of diabetes in **ReoPro** arms **compared** to placebo. (See Figure 3)

Forty-eight percent ofpatients in **the trial** had a history of prior MI. Endpoint events are consistently **reduced in** both patients **with** and **without** prior **MI,** and among **patients with prior MI,** whether the **MI occurred** at **any point, 7 days or more prior.** Patients with *a* **history** of MI within the prior 7 days had a somewhat higher event rate in the placebo arm (14.7 **%), but demonstrated** significant 30day endpoint reductions in both **ReoPro** arms. Patients with **MI** between 8-30 days prior were the smallest subgroup; nonetheless, a trend to reduction of primary endpoints was also seen in these patients. (See Figure 3)

Figure 3 Primary Endpoint at 30 Days By Clinical Risk Factors

Death, MI or **Urgent Revascularization** through **30** Days
by Cardiovascular History and Other Associated **Risk** Factors

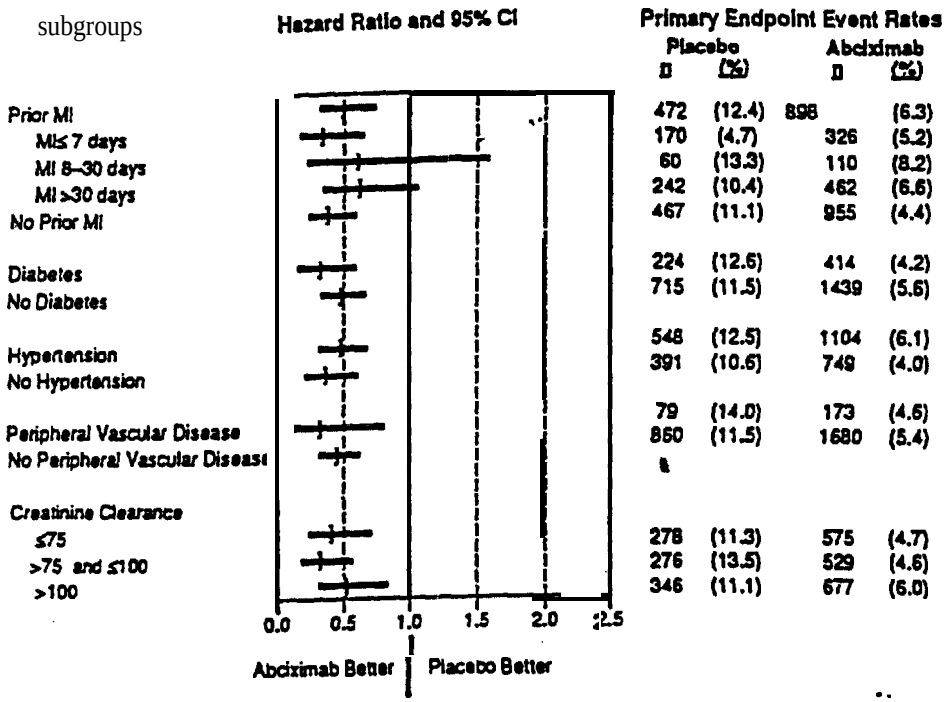


Figure 3 **Hazard Ratios** and **the** 95% **Confidence Intervals (CI)** for **Death,** MI or **Urgent Revascularization** by **Cardiovascular History and** Risk **Factors. The** number of **patients and the event rates are shown** on **the** right side for **each clinical** event according co **treatment** group. **Hazard ratios <1** indicarc **abciximab** is **better** and **hazard** ratios **>1 indicate** that **placebo** is **better.**

d. Type of MI

Clear trends toward-reduction of all types of MI in the ReoPro treated patients are seen, particularly for large non-Q wave MI, which comprised *two-thirds* of all MI during the 30 day follow up. The number of Q wave MI is reduced in the ReoPro treated arms, but is too small to reach statistical significance (see Table 16).

Table 16 Patients With Endpoint MI During 30 Day Followup

	Placebo n=939	ReoPro Lo Hep n=935	ReoPro Std Hep n=918
All MI n %	81 8.6 %	34 3.6 %	35 3.8 %
Q Wave MI n %	7 0.7 %	4 0.4 %	4 0.4 %
Large non Q[1] n %	56 5.9 %	19 2.0 %	23 2.5 %
Small non Q n %	18 1.9%	11 1.2 %	8 0.9 %

[1] Includes during (95) and after (3, all placebo) index hospitalization

Reviewer's Comment: The benefit was seen more in large non Q wave MI in EPILOG, as has been seen in the EPIC trial. Eighty percent of the MIs occurring during the study period in EPIC were non Q wave; 90% were non Q wave in EPILOG. Both Q Wave and NonQ wave MIs were reduced in EPIC with ReoPro treatment.

e. Cause of Death

At the 30day assessment the number of deaths was small in all arms. There wen mon cardiac deaths in tbe placebo arm than in the ReoPro arms combined. Three deaths were due to ICH; all in the ReoPro arms. More were due to definite or observed MI in the placebo patients (see Table 17).

Table 17 Cause of Death at 30 Days

	Placebo n=939	ReoPro Lo Hep n=935	ReoPro Std Hep n=918
Cardiac	5	2	2
Intracerebral Hemorrhage	0	1	2
Unknown	2	0	0
Total	7	3	2

f. Primary Endpoint by Indication for PTCA

Consistent results were seen for patients with unstable angina, recent Ml (defii as MI occurring between 24 hours and 7 days prior) and for stable angina and other indications (includes chronic stable angina or a positive functional test as the indication for the procedure) on both death and MI and death, MI and urgent revascularization at 30 days. Primary endpoint rates were significantly reduced for Abciximab treated patients compared to placebo in both patients with unstable angina and stable angina or positive functional tests. Results trended favorably for patients with recent MI (see Table 18).

Although there wen a modestly higher percentage of patients in the placebo arm with unstable angina compared to the percentage in the Abciximab treated arms (see Table 1, earlier), as the event rates were comparable for patients with unstable angina, recent MI, and stable angina/other indications, this does not affect the overall endpoint results.

Table 18 Composite Primary Endpoint at 30 Days by Indication for PTCA

Deaths, MI, or Urgent Revascularizations	Placebo n=939	ReoPro Lo Hep n=935	ReoPro Std Hep n=918
Patients with Unstable Angina	474	434	420
Events	57	21	21
%	12.2 %	4.8 %	5.0 %
Patients with Recent MI	189	200	190
Events	21	15	8
%	11.1 %	7.5 %	4.2%
Patients with Chronic Stable Angina and Positive Functional Tests	276	301	308
Events	31	12	20
%	11.3 %	4.1 %	4.1 %

g. Primary Endpoint at 30 days by type of device used

Most patients were treated with balloon angioplasty only. Event rates were higher in patients treated with STENT and rotational or other atherectomy, but consistent trends were seen in reduction of endpoint rates in the Abciximab arms compared to placebo. Table 19 presents a listing of event rates by type of device used in the index procedure.

Table 19 Composite Primary Endpoint at 30 Days by Type of Device Used

Deaths, MI, or Urgent Revascularizations	Placebo n=939	ReoPro Lo Hep n=935	ReoPro Std Hep n=918
Patients with Balloon Only	705	751	702
Events	48	20	21
%	6.9 %	2.7 %	3.0 %
Patients with STENTs	144	100	138
Events	28	7	10
%	19.5%	7.0 %	7.2%
Patients with Rotational or Other Atherectomy	57	56	56
Events	10	4	4
%	19.2 %	8.2 %	8.2 %

h. Primary Endpoint at 30 Days by Procedural Factors and Lesion Characteristics
The sponsor has provided an exploratory analysis defining hazard ratios for subgroups of patients by certain procedural factors and by complexity of the lesion as designated by the investigators at randomization. Clear benefit is demonstrated for patients with one or man than one segment treated, for patients with and without prior PTCA, and for patients with and without thrombus in the lesion to be treated. Event rates in the placebo arm are low for patients with Type A lesions, particularly Type A de novo lesions, and for patients with only 1 Type B characteristic. For those subgroups, there does not appear to be a demonstrable benefit from the use of Abciximab in this sample. (See Figure 4).

Death, MI or Urgent Revascularization through 30 Days
by Procedural Factors Influencing Clinical Outcome

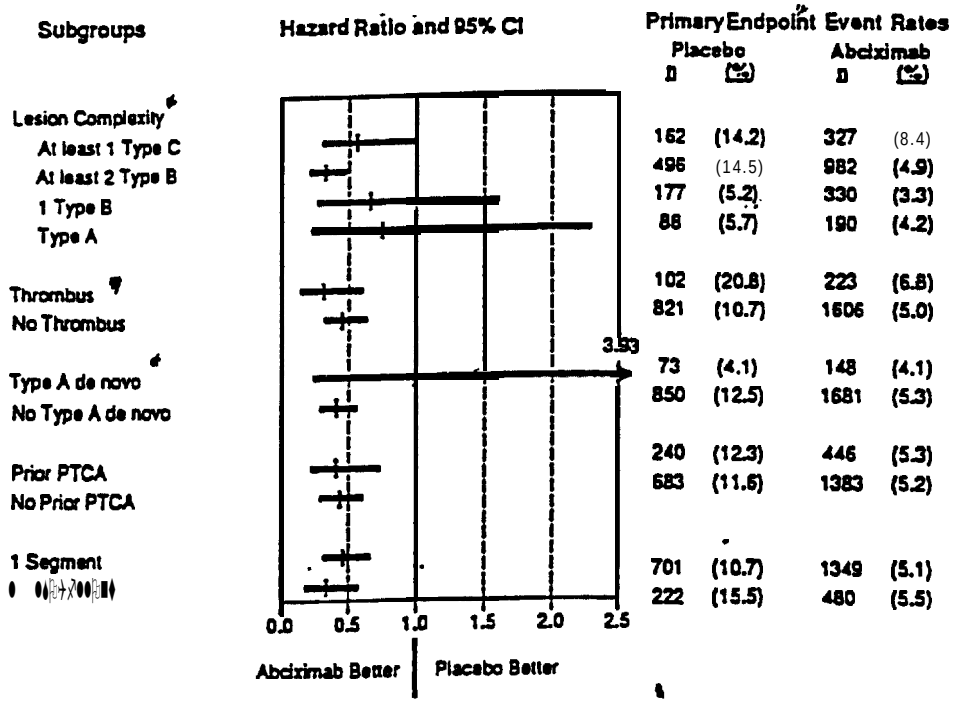


Figure 4 Hazard Ratios and the 95% Confidence Intervals (CI) for Death, MI or Urgent Revascularization by Procedural Factors Influencing Clinical Outcome. The number of patients and the event rates are shown on the right side for each clinical event according to treatment group. Hazard ratios <1 indicate abciximab is better and hazard ratios >1 indicate that placebo is better. * CRF data

i. Primary Endpoint at 30 days by Study Site

Results are fairly consistent among sites of large enough size to permit comparison. Table 20a shows event rates by whether sites were academic or non-academic medical centers. Of interest is that placebo event rates were lower at academic medical centers, while the rates in the Abciximab treated patients were similar at both academic and non-academic centers.

Reviewer Comment: It may be that the academic centers enrolled a higher proportion of patients with very low risk status, or that ancillary care at the academic sites contributed significantly to lower event rates.

Table 20a Primary Endpoint at 30 days by Academic and Non-Academic Centers

Deaths, MI, or Urgent Revascularizations	Placebo n=938	ReoPro Lo Hep n=935	ReoPro Std Hep n=918
Academic Centers n Events %	276 24 8.7 %	272 12 4.4 %	266 15 5.6 %
Non-Academic Events % Centers n	662 85 12.8 %	36 665.4 %	652 34 5.2 %

The proportion of patients designated as high and low risk by the as randomized classification and the primary endpoint event rates for each subgroup, by academic and nonacademic sites, are shown in Table 20b. The placebo event rate for the patients identified as low risk at the academic centers is extremely low, while those identified as low risk at the nonacademic centers have an event rate more comparable to the overall rate.

Table 20b Primary Endpoint by Risk Status at Randomization and by Academic and NonAcademic Centers

Deaths, MI, or Urgent Revascularizations	Placebo LOW RISK n = 337	Placebo HIGH RISK n = 601	ReoProLoHep LOW RISK n = 333	ReoProLoHep HIGHRISK n-602	ReoProStdHep LOW RISK n = 338	ReoProStdHep HIGH RISK n = 590
Academic Centers n Events %	100 2 2.0 %	176 22 12.5 %	99 1 1.0 %	173 11 6.4 %	93 4 4.3 %	173 11 6.4 %
Non-Academic Centers n Events %	237 29 12.2 %	425 56 13.2 %	234 7 3.0 %	429 29 6.8 %	235 12 5.1 %	417 22 5.3 %

The same analysis by CRF risk classification (made retrospectively, after the procedure) is shown in Table 21. By this classification, the placebo event rate in the patients identified as low risk is consistently lower than that for the patients identified as high risk at both academic and nonacademic centers.

Table 21 Primary Endpoint by Risk Status per CRF and **by Academic and NonAcademic Centers**

Deaths, MI, or Urgent Revascularizations	Placebo LOW RISK n = 176	Placebo HIGH RISK n = 747	ReoProLo Hep LOW RISK n= 186	ReoProLoHep HIGH RISK n = 738	ReoProStdHep LOW RISK n = 211	ReoProStdHep HIGH RISK n = 700
Academic Centers n Events %	64 1 1.6 %	207 23 11.1 %	62 2.9 %	200 10 5.0 %	62 2.9 %	205 12 5.8 %
Non-Academic Centers n Events %	112 7 6.3 %	540 77 14.3 %	117 4 3.4 %	538 29 5.4 %	118 6 5.1 %	527 28 5.3 %

Reviewer Comment: The event rate for low risk patients in the placebo group as identified at academic centers by either randomization or CRF appears similar, and substantially lower than the overall event rate. The placebo event rate for low risk patients at nonacademic centers appears as high at randomization as the rate for the high risk patients: it is ***substantially lower by the CRF assessment, If event rates are used as an indicator of risk, then perhaps academic investigators predicted risk status more accurately at randomization than did itivestigators at non-academic centers. However, the procedural outcome, and in some cases the patients's clinical course, were known at the time of CRF completion, which may have biased that*** *assessment.*

2. 6 Month Primary Endpoint

a. Deaths **by Cause @ 6 months**
There were a total of 39 deaths over the 6 month **followup** period in the trial. There were 21 cardiac deaths, distributed evenly (7 each) per arm.

There were 3 deaths attributed to hemorrhagic stroke, none in the placebo **arm,** 1 in the **ReoPro Low** dose arm and 2 in the Abciximab Standard Dose Heparin arm. In addition, the **ReoPro** Std Dose **arm** had 1 other vascular death.

Non-cardiac medical deaths occurred infrequently, 1 per arm. There was one non-cardiac **trauma-**related death, in the placebo arm. **There** were 7 **"unknown"** causes of death in the placebo arm; patients **who** died after **hospital discharge,** for whom the cause of death was undetermined. There were a total of 3 **unknown** causes of death in the Abciximab **arms,** 1 in the Low Dose and 2 in the Standard Dose Heparin arms.

b. By Risk Classification
When the 6 month primary endpoint is examined by randomized risk classification, the **results** are variable. There are significantly less events in high risk patients in the **ReoAPro** Standard Dose Heaprin arm, and a trend toward less events in low risk patients in th **eReoPro** Low Dose Heparin arm by this classification (see upper ***portion*** of table 22). This endpoint includes any **revascularization**procedures.

The benefit seen on the primary 30 day endpoint in Abciximab treated patients is *seen to* be sustained at 6 months in both high and low risk patients, as they were identified at randomization. This endpoint includes death, MI, and urgent revascularizations (see lower portion of table 22).

Table 22 Death, MI, *Or* Repeat **Revascularization During 6 Month Follow-Up By Risk Classification At Randomization**

Death, MI or Repeat Revascularization	Placebo n=939	ReoPro Lo Hep n=935	ReoPro Std Hep n=918
High Risk Patients	602	602	590
Events	166	153	132
%	27.7 %	25.4 %	22.6 %
p value		0.43	0.04
Low Risk Patients	337	333	328
Events	75	59	71
%	22.4 %	17.8 %	21.7 %
p value		0.15	0.85
Death, MI, or Urgent Revascularization			
High Risk Patients	602	602	590
Events	98	61	53
%	16.3 %	10.2 %	9.0 %
p value		.002	.0002
Low Risk Patients	337	333	328
Events	40	17	23
%	11.9%	5.1 %	7.0 %
p value		,002	.035

Event rates from Kaplan/Meier/ Logrank test time to event analysis

By the CRF risk classification, there is evidence of benefit in the patients assessed as high risk on both the 6 month primary endpoint including all revascularization procedures, and the 6 month composite including only urgent interventions, but the results for the low risk patients do not show a difference (see Table 23).

Table 23 Death, %51, Or Repeat Revascularization During 6 Month Follow-Up By CRF Risk Classification

Death, MI or Repeat Revascularization	Placebo n=939	ReoPro Lo Hep n=935	ReoPro Std Hep n=918
High Risk Patients Events % p value	748 207 27.7 %	738 174 23.6% 0.08	732 167 22.8 % 0.04
Low Risk Patients Events % p value	176 31 17.6 %	186 33 17.7 % 1.0	175 34 19.4 % 0.7
Death, MI, or Urgent Revascularization			
High Risk Patients Events % p value	748 124 16.6 %	738 63 8.5 % < .0001	732 62 8.5 < .0001
Low Risk Patients Events % p value	176 13 7.4 %	186 12 6.5 % 0.8	175 14 8.0 0.8

1 Event rates from Kaplan/Meier/ Logrank test time to event analysis
2 2 sided P values based on Fisher exact test, per CBER Biostat analysis

c. By Type of MI

Non Q wave **MI were reduced by more than** half **in** each **Abciximab treated** arm compared to placebo. There was not a significant reduction in Q wave **MIs,** but the numbers of events were small (Table 24).

Table 24 Patients With Endpoint MI During 6 Month Followup *

Events	Total n=2792	Placebo n=939	ReoPro Lo Hep n=935	ReoPro Std Hep n=918
All MI %	188	93 9.9 %	47 5.0 %	48 5.3 %
Q Wave %	40	15 1.6 %	12 1.3 %	13 1.4 %
All non Q %	151	79 8.4%	36 3.9 %	36 3.9 %

*Kaplan/Meier/ Logrank test; some patients counted in **both** Categories

B. Exploratory Analyses on Secondary Endpoints

1. Death, MI and repeat revascularization at 30 days
A significant difference in all repeat revascularizations at 30 days (that is the 6 month primary endpoint at the 30 day timepoint) was seen in Abciximab treated arms compared to placebo. These trends were also seen in endpoints with target vessel procedures and repeat revascularizations for clinically significant ischemia, as shown in Table 25 below.

Table 25 Death, MI And Revascularization Procedures At 30 Days

Patients w Death, MI and...		Total	Placebo (n=939)	Reo Lo Hep* (n=935)	Reo Std Dose* (n=918)
Repeat Revascularization	n	277	129	74	74
	%		13.9 %	8.0 %	8.2 %
TargetVesselRevascularzn	n	250	125	61	64
	%		13.4 %	6.7%	7.0 %
Revascfor Clin Sig Ischemia	n	236	116	60	60
	%		12.5 %	6.5 %	6.6 %

Logrank test, all sig @ <.001 +Patients may be counted in more than one analysis

2. All revascularizations, urgent and non-urgent and CABG at 6 months
The ReoPro arms showed a marked decrease in urgent procedures; however, as urgent procedures only comprised one-fourth of total revascularization procedures done over the 6 month period, there was no significant difference in total repeat procedures among treatment arms (see table 26). Most revascularization procedures were non-urgent. Non-urgent procedures were actually slightly increased in the ReoPro Lo Dose arm compared to the placebo arm.

There is a small trend toward less target vessel revascularizations and revascularization procedures for clinically significant ischemia in the Abciximab treated patients at 6 months, but no significant difference was seen on these rates among Abciximab treated patients compared to placebo treated patients (Table 26 also).

Reviewer's Note: The factors responsible for the "catching up" of non-urgent revascularization rates in the Abciximab treated arms are not clear. The sponsor has suggested this may be due to the inability of the Abciximab infusion for a X2-hour period to retard the natural progression of the underlying atherosclerotic disease in both the treated vessel and other vessels.

Table 26 Patients With Revascularization Procedures at 6 Months

Patients w events	Total (n=2792)	Placebo (n=939)	Reo Lo Hep(n=935)	Reo std Hep(n=918)
All Repeat Revascularizations				
n	523	180	176	167
%		19.4 %	19.0 %	18.4 %
95 % CI				
p value[2] (excludes staged procedures)[1]			0.354	0.260
Urgent Revascularization				
n	124	63	29	**32**
%		6.7 %	3.1 %	**3.5 %**
95 % cl		(5.11 - 8.31)	(1.99 - 4.21)	(2.30 - 4.67)
p value			**<.001** (= .0004)	**<.001** (= .0021)
Non-Urgent **Revascularization**				
n	421	127	155	139
%		13.8 % (11.34 - 15.71)	16.7 %	15.4 %
pvalue			0.037	0.165
Target vessel **Revascularization**				
n	472	168	157	147
%		18.1 %	17.0 %	16.2 %
p value			0.206	**0.117**
Revasc for Clin Signif Ischemia				
n	460	159	**152**	149
%		17.1 %	16.4 %	16.5 %
p value			0.2%	0.301

1 A total of 17 procedures were staged, 9 placebo, 5 RLD and 8 RSD

2 p value from chi square test per CBER Bostatistics review

Similarly, urgent CABG rates occurred at markedly lower rates in Abciximab treated patients (see Table 27). Non-urgent CABG rates were not different among treatment arms, however.

Table 27 Patients Who Had CABG During 6 Month Follow-Up[1]

	Placebo N = 939	Reo Lo Hep N = 918	Reo Std Hep N = 935
Patients w CABG n % P value[1]	70 7.5 %	56 6.0 % 0.094	56 6.2 % 0.119
Urgent CABG n % p value[1]	22 2.4 %	6 0.6 % 0.001	9 1.0 % 0.011
Non-Urgent CABG n % p value[1]	48 5.2 %	50 5.4 % 0.429	47 5.2 % 0.491

1 Rates and p values from Log-Rank Time to Event Analysis

Reviewer's Note: Again, this differential effect on urgent and non-urgent procedures may be due to progression of atherosclerosis despite the effect on thrombosis in patients treated with Abciximab which reduces the number of urgent procedures performed in those patients.

VI. SAFETY RESULTS

.A. Prespecified Primary Analyses

The two primary safety endpoints prespecified were:

1) Death and hemorrhagic stroke incidence over the 6 month duration of the trial, and

2) Major non CABG associated bleeding rates during hospitalization or within the first 7 days of hospitalization

1. Death and hemorrhagic stroke incidence over **the 6 month duration of the trial** There was no significant difference in the incidence of death and hemorrhagic stroke between treatment arms. A small number of events occurred in each arm. Table 28 shows rates of death and hemorrhagic stroke at 6 months and at 30 days in all treatment arms.

Table 28 Death and Hemorrhagic Stroke at 6 Months and at 30 Days

	Placebo N = 939	Reo Lo Hep N = 935	Reo Std Hep N = 918
Death and Hem Stroke @ 6 mo	16	11	15
Death	16	10	13
Hem Stroke	0	1	2
Death & Hem Stroke @ 30 days	7	4	5
Death	7	3	4
Hem Stroke	0	1	1

Note: this table only includes hemorrhagic stroke. There were 2 intracranial bleeds (one subdural and one both subdural and subarachnoid) in patients in the ReoPro + Std Dose Heparin arm occurring at 10 hours and at 8 hours, which are not listed hen). Additionally, 1 patient in the ReoPro Std Dose arm had a hemorrhagic stroke (cerebellar lacune) at 18 days, which was not reported until after the 30 day database lock.

2. Major non **CABG** associated **bleeding rates during hospitalization or within the first 7 days of hospitalization**

Major non CABG bleeding rates were not significantly different in the ReoPro Low Dose Heparin arm from placebo, (10 in each arm) but the rate in the ReoPro Standard Dose Hcparin arm was almost doubled (17), although not statistically significant ($p = 0.18$). Minor non CABG bleeding was significantly increased in the ReoPro Standard Dose Heparin arm compared to placebo.

B. All Other **Prespecified Safety Analyses**

1. Bleeding

a) Major **and minor overall** (this includes both bleeding associated with and not associated with CABG) There was no significant difference in the proportion of major bleeds among arms. There was a clear trend to less major bleeding in the ReoPro Low Dose arm compared to placebo, though it was not statistically significant. ReoPro with Standard Dose heparin had a few more major bleeds than the placebo arm (standard dose heparin alone); this difference was not significant.

Minor bleeds are significantly increased (doubled) in the ReoPro with-Standard Dose hcparin arm, however. It should be noted that what is termed "minor" bleeding in this trial actually represents a substantial loss of blood. No significant difference appears between minor bleeding in the ReoPro Low Dose and placebo arms. The number and proportion of patients with insignificant or no bleeding is highest in the ReoPro with Low Dose Heparin arm.

Table 29 Major And Minor Bleeding Overall (includes CABG related bleeding)

Patients w events	Placebo N = 939	Reo + Lo Hep N = 918	Reo + Std Hep N = 935
Major or Minor Bleeding n %	64 6.8 %	56 6.0 %	100 10.9 %
Major bleeding n %	29 3.1 %	19 2.0 %	32 3.5 %
Minor bleeding n %	35 3.7 %	37 4.0 %	68 7.4 %
Insig or No Bleeding n %	834 (189 + 645)# 88.8 % (20 + 68)#	848 (281 + 567)# 90.7 % (30 + 60)#	780 (288 + 492)# 85.0 % (31 + 53)#
Patients not eval'd	41 4.4 %	31 3.3 %	38 4.1 %

Numbers in parens indicate the number and percentages of patients with insignificant + no bleeding)--from CBER Biostatistics review

Reviewer's Note: In the EPIC trial, of 2099 patients, 222 had major bleeds-99 in the bolus and infusion group (14 %), 77 in Bolus only, and 46 in placebo (6.6 %). The risk was increased in patients ≥ 65 yrs, weight < 75 kg, acute MI w/in 12 hrs prior to PTCA, prolonged or failed PTCA, history of GI Bleed Bleeding rates in all arms in the EPILOG trial were remarkably reduced compared to those in the EPIC trial, probably owing to the combination offactors that were changed in the EPLLOG trial; e.g., the weight adjustment of heparin and ReoPro dosing, the decreased duration of heparin treatment, and the more stringent requirements for access site care, in addition to the use of the low dose heparin in that treatment arm. Heparin weight adjustment, duration and dose appear to have been the most important factors.

(b) By Subgroup
No significant differences were seen in bleeds by weight or gender or age. See discussion in next section of non - CABG associated bleeding by these variables'.

2. CABG and Non-CABG Bleeding

(a) Overall

The major non CABG bleeds in the ReoPro low dose heparin arm were equal in number and percentage to those in the placebo arm. As noted under A. above, there were a **greater** number of major non CABG bleeds in the ReoPro Std Dose heparin arm (nearly double **the placebo** rate), but the numbers were too small to reach statistical significance.

Minor non **CABG bleeds** were similar in the **ReoPro** Low Dose heparin arm to the placebo rate, and were significantly increased to more than double the placebo rate in the ReoPro Standard Dose heparin arm. (See Table 30 below)

Table 30 Non CABG Bleeding

Patients with events	Placebo n = 939	Reo Lo Hep n = 935	Reo Std Dose n = 918
Significant Bleeding	42 4.5 %	47 5.1 %	87 9.5 %
Major bleeds n % P value	10 1.1 %	10 1.1 %	17 1.9 % 0.178
Minor bleeds n % p value	32 3.4 %	37 4.0 %	70 7.6 % < 0.001

Reviewer's Note: Exploratory analyses revealed a number of patients in all arms who had "insignificant" bleeds that did not meet the criteria for a minor or major bleed). When these are added, the percentage of patients with any bleeding increases to 2.5 % placebo, 35 % ReoPro Lo Dose Heparin, and 41 % in the ReoPro Standard Dose Heparin arm. (source: CBER Biostatistics Review)

Table 31 presents the bleeding associated with CABG by treatment arm. This bleeding accounted for over half of the major bleeding in the trial.

Table 31 Bleeding Associated With CABG

Patients w events	Placebo	Reo Lo Hep	Reo Std Dose
Patients w/ CABG	26	11	16
Any Bleeding	23 88 %	11 100 %	16 100 %
Major bleeds n %	19 73 %	9 82 %	16 100 %
Minor bleeds n %	4 15 %	2 18%	0 0%

Reviewer's Note: All patients who had CABG in the ReoPro arms had some form of significant bleeding, as did nearly all patients in the placebo arm. Note that all CABG patients in the ReoPro Standard Dose arm had Major bleeds.

Most patients in the EPIC trial who underwent CABG (33 in each, placebo & bolus - infusion arms) had major bleeding (73 % placebo, 78 % bolus - infusion). These results are not markedly different. There were fewer patients going to CABG in the ReoPro treated arms than in ***the placebo arm however, in both EPIC and EPILOG.***

3. Transfusions

The number of patients receiving transfusion of **PRBCs** or whole **blood was small in the EPILOG** trial. Less patients in the **Abciximab** Low Dose Heparin arm received transfusions compared to either placebo or Abciximab plus **Std** Dose Heparin (patients in the placebo arm also received standard dose heparin (see Table 32).

Table 32 Transfusions

	Placebo (n = 939)	ReoPro Lo Dose (n = 935)	ReoPro Std Dose (n = 918)
PRBCs or Whole Blood	37	18	30
Non - CABG	10	6	7
Platelets	10	8	15
Non - CABG	1	0	1

The most common reasons cited for transfusion was preparation of the patient for CABG or a decrease in Hemoglobin or Hematocrit. Platelet transfusions were also uncommon, particularly among patients not undergoing CABG.

(b) Bleeding by Age, Gender, and Body Weight

No differences of importance were seen in rates of major bleeding in either women or in older patients in the Abciximab and Low Dose Heparin arm compared to placebo.

Reviewer's Note: Bleeding rates in women and in patients over 65 ***years of age were substantially higher than among other age and gender groups among patients in all arms in the EPIC trial.***

There were higher rates of major non-CABG bleeds among women over 65 years in the arms treated with Standard Dose Heparin, but the numbers of patients in this subgroup were relatively small. A notable, but not significant difference was seen in both women and men **≥ 65** years in the **ReoPro** Standard Dose Heparin arm. **Table 33** presents major non-CABG associated bleeding by gender and **age.**

No significant differences were seen in any weight subgroups among the treatment arms in major non-CABG bleeding (see Tables 34 and 35).

Table 33 Major Non CABG Bleeds By Gender And Age

Patients w major bleeds	Placebo	Reo Lo Hep	Reo Std Dose
Men < 65 yr n % p value[1]	461 3 0.7 %	465 4 0.9 % 1.00	440 4 0.9 % 0.720
Men ≥ 65 yr n % p value[1]	213 2 0.9 %	203 2 1.0 % 1.00	230 6 2.6 % 0.288
Women < 65 yr n % p value	137 2 1.5 %	141 3 2.1 % 1.00	128 1 0.8 % 1.00
Women ≥ 65 yr n % p value[1]	128 3 2.3 %	126 1 0.8 % 0.622	120 6 5.0 % 0.321

*1 p value is compared to placebo; based on log rank time to event analysis

'able 34 Major Non CABG Bleeds By Body Weight

Patients w major bleeds	Total	Placebo	Reo Lo Hep	Reo Std Dose
Patients ≤ 75 kg n % p value1	792 11 1.4 %	282 3 1.1 %	272 2 0.7 % 1.00	238 6 2.5 % 0.3 13
Patients > 75 to < 90 kg n % p value[1]	988 15 1.5 %	308 3 1.0%	326 5 1.5 % 0.726	354 7 2.0 % 0.352
Patients ≥ 90 kg n % p value[1]	1010 11 1.1 %	348 4 1.1 %	336 3 0.9 % 1.00	326 4 12 % 1.00
Wgt unknown	2	1	1	0

Log rank time to event analysis sig <.05

Patients over 80 kg received a fixed dose regimen of Abciximab. When data are analyzed by weight subgroup using the **80-kg** cutoff, no significant differences in the rates on bleeding are seen when patients < 80 kg are compared to patients 2 80 kg. (See table 35 below).

Reviewers ' Note: All patients in the trial had weight adjusted heparin doses. Over half the patients in the trial (1,707 patients) fell into the group weighing ≥ 80 kg, and received a fixed dose of 10 ug/min Abciximab.

Table 35 Major Non CABG Bleeds By Body Weight

Patients w major bleeds	Placebo n = 939	Reo Lo Hep n = 935	Reo Std Dose Hep n = 918
Patients < 80 kg n %	378 3 0.8 %	367 5 1.3 %	338 7 2.1 %
Patients 2 80 kg n %	560 7 1.3%	567 5 0.88 %	580 10 1.7 %

4. Timing of Bleeds

(a) The CEC analyzed bleeding by time of occurrence. Then were more cases of major bleeding occurring during the period from baseline to 36 hours in the Abciximab Standard Dose Heparin arm. More of the minor bleeding in all arms occurred within the first 36 hours, as well, more so in both of the Abciximab arms than placebo. More patients in the placebo arm were receiving heparin for a longer time period, suggesting a correlation of later bleeding to extended heparin usage.

(b) Hemoglobin changes and transfusions within 48 hrs of end of study agent in patients undergoing CABG were greater in patients treated with the standard dose heparin regimen than in the Abciximab-low dose heparin arm. The Abciximab treated patients who subsequently went to CABG were usually treated with platelet transfusions to reverse the antiplatelet effects prior to surgery. Heparin, however, was continued. Bleeding complications were frequent in these patients. There were more transfusions in Placebo and Abciximab Standard Dose Heparin patients, suggesting a stronger relationship of bleeding during this time period to heparin usage.

Reviewer's Note: It** is **difficult to identify wfth certainty which of the agents is more responsible for non-CABG related bleeding complications by assessment of timing during the period beyond administration of the study agent. The effects of Abciximab may be present on platelets for up to 15 days after administration: and the patients are also still being treated with aspirin.

5. Bleeding By Location

The most common location of both major and minor bleeding events was at the femoral arterial access site. Approximately 70 % of major bleeding occurred at the femoral access site in all treatment arms, as did 62 to 83 % of minor bleeding. More patients in the ReoPro treated arms had minor arterial access site bleeding only than did patients in the placebo + Std dose heparin (over 80 % compared to 60 %). More patients in the placebo + Std dose heparin and the ReoPro + Std Dose Heparin arms had either major or minor bleeding at sites other than the arterial access site, including GI and GU bleeding, and a single case of major ntroperitoneal bleeding occurred in a placebo patient.

See Table 36 for a listing of major and minor bleeds by location.

Reviewer's Note: The ***largest proportion of major bleeding occurred at the femoral and other arterial access sites in patients in the EPIC trial also. Compared to the EPIC trial, there were many fewer sheath*** site ***and GI, GU and retroperitoneal bleeds in the patients in the EPILOG trial*** in *all treatment* ***arms. Major GI, GU, sheath site and retroperitoneal bleeding rates among Abciximab treated patients in EPIC were also substantially increased compared to placebo treated patients.***

Table 36 Major And Minor Non CABG Bleeds By Location

Location	Placebo n = 939		Reo Lo Hep n = 935		Reo Std Dose Hep n = 918	
	Major	Minor	Major	Minor	Major	Minor
All Non CABG Bleeds	10	32	10	37	17	70
Femoral Access Site	7	20	7	31	12	58
Other Arterial Site	3	2	3	2	0	0
GI	1	6	2	1	1	9
GU	1	4	0	S	2	9
Retroperitoneal	1	0	0	0	0	2
Intracranial	0	-	1	-	2	-
Other*	1	1	0	2	S	5
Dec Hb or Hct only	1	9	2	6	s	20

* other includes eye, ear, nose, throat, pulmonary and pericardial sites

6. Stroke and ICI-I by Timing of Occurrence

The incidence of stroke and intracranial bleeding was not statistically different *among* treatment arms, although more events occurred in the Abciximab treated arms (see table 37). Events occurring during the index hospitalization or within the first 14 days after randomization are the most relevant to treatment with Abciximab, as the agent is expected **to be cleared from the platelets by the end of** that period. (see Table 38).

Reviewer Note:

Rates of intracerebral hemorrhage and *nonhemorrhagic stroke in* ***the EPIC and CAPTURE trials were not significantly different between Abciximab and placebo treated patients; the integrated data shows events in 7 of*** 2,225 **(0.31 %) placebo patients and 10 of 3,112 (0.32 %) Abcirimab-treated patients across all 3 trials in the 30 day period** *after randomization. The rates of* **ICH alone were 0.13 % in placebo patients and** 0.19 % **in Abciximab patients.**

This study was not powered to adequately detect a difference in events *of* ***such low frequency, and a real difference can not be ruled out entirely on the basis*** *of* ***these data. Further examination*** *of the clinical histories of patients* ***with ICH in the EPILOG study is suggestive*** *of an additive* ***effect*** *of* ***heparin, aspirin and Abciximab on intracerebral bleeding, particularly when standard dose heparin is used and the target ACT is high.***

Table 37 Stroke Or ICH Within 6 Months Confirmed By Neuro CEC

Patients with events	Placebo	Reo Lo Hep	Reo Std Dose
Any Stroke or ICH n %	1 0.1 %	5 0.5 %	7 * 0.7 %
Hemorrhagic Stroke n %	0	1 0.1 %	2 * 0.2 %
Other # n %	0	1 0.1 %	2 0.2 %
Non hem Stroke n %	1 0.1 %	3 0.3 %	4 * 0.4 %

1 pt had both a nonhemorrhagic and hemorrhagic stroke
subdural hematoma in 2 patients

The following table presents the incidents of hemorrhagic and nonhemorrhagic stroke by timing and survival status for each treatment arm. There were 4 patients who were found by the Neuro CEC to have had events but were without adequate documentation to classify the events in the Low Dose arm, and 2 each in the placebo and Std Dose arms. Those patients are included in the table.

Table 38 Timing Of Neuro Events Within 6 Months Reviewed By CEC (excludes events lassified by CEC as TIA and as no event)

Events Reviewed	Placebo (n =3)	ReoPro Lo Hep (n = 10)	ReoPro Std Hep (n = 9)	Outcome at 6 mo
Within Index Hospitalization				
Nonhem Stroke	–	–	–	
ICH	–	1 (2 hr)@	2 (8[!], 10 hr)	All Death
Unclassified	–	–	–	–
To 30 days				
Nonhem Stroke	–	1 (8 day)*	1 (28 day)	Alive, Alive
ICH	–	–	2 (18, 28 day) •	Both Alive
Unclassified	–	–	–	–
To 6 months				
Nonhem Stroke	1 (158 day)	2 (33.85 d)	3(36, 76, 186 d)	All Alive
ICH / ICB		1 (72-78d)^		Alive
Unclassified	2 (2 mo, 5-6 mo)		1 (83 d)	Death, Alive
		5 (40, unknown, 127+, 181 d, 5 mo)		All Alive

Subdural and Subarachnoid
@ Assoc w/ MI; cause of death uncertain
*Basal ganglia Lacune
. Pt @ 28 days had both hemorrhagic and nonhemorrhagic stroke Pt at 18 days had a Cerebellar bleed
"Subdural Hematoma
+ Patient died at day 280 of a second stroke

The incidence of intracerebral bleeding was low in all treatment arms, however, there were no cases occurring during the index hospitalization in the placebo arm in this trial. There were 2 cases of ICH during the index hospitalization in the ReoPro Standard Dose Heparin arm. In both cases, the ACT during the procedure was quite high (394 and 405 were the maximal values observed), and it is likely the heparinization contributed to the bleeding. An interaction with the antiplatelet effects of Abciximab is also possible, as both bleeds occurred during the 12 hour Abciximab infusion time.

There was one case of ICH occurring during the index hospitalization in the ReoPro-Lo Dose Heparin arm, a right frontal subdural hematoma, which was surgically evacuated, but unsuccessful, and the patient expired. (It is not clear whether the ICH was the cause of death as the patient also sustained an MI.) The patient's maximal ACT was 250 during the procedure, and the platelet count was normal. It is likely the bleed in this case was due to a combination of the anticoagulation and antiplatelet effects of heparin, aspirin and Abciximab.

Reviewer Comment: These data are suggestive of additive effects of Abciximab, heparin, and aspirin in causing intracerebral bleeding. Taken together with the other bleeding data from this trial, these data strongly suggest that the combination of Abciximab and standard dose heprin should be avoided because of the increased bleeding risk..

7. Effect on Platelet Counts

Overall, 2.2 % of patients in the trial had thrombocytopenia. The median percent decrease was only slightly greater in ReoPro arms from study agent start until discharge 14%, 15 % vs 11 % placebo, and within 12 hours of start of study agent (1 1%, 12 % vs 8 % in placebo). Between 12 hours and the time of hospital discharge, the decrease was less in the ReoPro Low Dose Heparin arm than in the placebo arm (6.9 % vs 8.8 %). Table 39 shows a greater number of patients in the Abciximab arms had platelets decreased under 100,000, but the Abciximab standard dose heparin arm had the largest number of patients with platelets less than 50,000. Note: 3 patients with platelets < 50,000 DIED (2 in the ReoPro Standard Heparin arm, 1 in the placebo arm).

Table 39 Patients with Thrombocytopenia

	Placebo (n = 939)	ReoPro Lo Dose (n = 935)	ReoPro Std Dose (n-918)
PLT < 100,000	14	23	24
PLT < 50,000	4	4	8

Reviewer Comment: These data suggest that while both heparin and Abciximab may contribute to thrombocytopenia, the combination of Abciximab with Standard Dose Heparin may be the most likely to cause severe thrombocytopenia and should be avoided.

8. Other Adverse Events

Only 1 major retroperitoneal bleed was seen in the trial; it occurred in the Placebo arm. There were 2 retropexitoneal bleeds that were classified as minor, in the ReoPro Standard Dose Heparin arm. There was no significant difference among treatment arms in other adverse events overall or in any organ system.

9. Relatedness to Study Drug

A total of 59 patients had serious adverse events that were considered reasonably related to study drug. The highest proportion occurred in the ReoPro Standard Dose Heparin arm (3.3 % vs. 1.5 % in the placebo arm, p = .0014. The proportion in the ReoPro Low Dose Heparin arm was not significantly higher than that in the placebo arm (2.2 %).

10. Treatment Discontinuations Due to Adverse Events

Overall 2 % of patients had the dose of study drug decreased or discontinued due to adverse events. Most cases were for bleeding. The incidence was lowest in the ReoPro Low Dose Heparin arm (1.4 %), and higher in the. placebo arm (1.8 %), and highest in the ReoPro Standard Dose Heparin arm (2.9 %).

11. HACA Results

Serum samples were obtained only on patients in the Angiographic Substudy and assessed for HACA response at baseline, 30 days, and 6 months. Of the total 286 patients in this substudy, there were 13 1 who were evaluable (had serum samples at all 3 timepoints and were treated with Abciximab). The total incidence of positive HACA responses in all Abciximab-treated patients who were evaluated was 6.1 % , or 8 of 131 patients. This included 5 (7.7%) in the Abciximab plus low dose heparin arm, and 1 (1.6 %) s in the Abciximab plus standard dose heparin arm, and 2 of 3 placebo patients who had received open label ReoPro during the index hospitalization. Titers were low; 1:50 in 3 patients, 1: 100 in 3 patients, 1:400 in 1 patient and 1: 1600 in 1 patient.

Reviewer's Note: Results in the EPIC trial indicated 6.5 % ***of patients developed HACA antibodies with similar followup. Values were drawn at 4 and I2 weeks post treatment,***

12. Readministration of Abcirimab

Abciximab was known to have been readminstered to 15 patients during the EPILOG study, 5 in **the** Abciximab-low dose Heparin arm and 10 in the Abciximab-Standard dose Heparin arm. The interval ranged from approximately 1 month to 6 months. There were 2 patients who had previously been treated with Abciximab in the EPIC trial who were randomized to the Abciximab plus standard dose heparin **arm** of the EPILOG trial and were HACA negative during EPIC trial followup.

An allergic reaction was observed in *one* patient **shortly** after the **initial** administration of Abciximab. The **reaction** resolved with treatment with **Benadryl** and steroids. Study drug was discontinued after the patient had received one hour of the planned **12** hour infusion. This patient was **readministered** Abciximab at 187 days post randomization, and no adverse events were noted.

One patient had face and chest redness with **pruritus** following **readministration** of Abciximab at 75 days post randomization for a repeat percutaneous intervention. The reaction required **no** treatment. This same patient had thrombocytopenia (nadir 73,000, resolved spontaneously) **after** initial administration of Abciximab during the initial hospitalization.

Reviewer's Note: Readministration of Abciximab without incident in the first patient discussed above suggests that the allergic reaction observed after the first treatment may have been due to another etiology. There is a possibility in the second case discussed above that an immune response secondary to readministration of Abciximab may have been responsible for the facial redness and pruritus seen. HACA data are not available on these patients.

13. Vital Signs and Laboratory Effects

No significant differences in among treatment arms **were** seen on any of the vital signs or laboratory parameters **measured**.

B. Exploratory Analyses

1. Effect of Sheath Removal and Heparin Duration on Bleeding

The protocol recommended removal of the arterial sheath within 6 hours after removal of completion of the index procedure **(guidewire** removal). Investigators frequently took the option of **continuing** the sheath in position for longer, **(n =** 1437 **≤** 6 **hrs, n =** 1140 **>** 6 hrs).

No significant difference are seen in the sponsor's analysis of bleeding events with sheath removal at **≤** *6* hours of guidewire removal or **>** 6 hours.

ACTs at sheath removal were largely below 175. However, sheath site bleeding was **more** common among patients with ACT greater than 175 seconds or **aPTT** greater than 50 seconds (see Table 40). Among patients whose **ACT** was above this level at the time of sheath removal, the rate of major sheath site bleeding complications was greater among **patients** in both Abciximab arms. The highest rates of sheath site bleeding were also seen in patients in the Abciximab standard dose heparin arm, irrespective of the ACT value.

Among patients whose ACT or **aPTT** met the protocol specified values prior to sheath **removal,** the incidence of sheath site bleeding was highest among patients in the abciximab plus standard dose **heparin** group (7.3 %) , lowest among patients in the (3.6 **%)** placebo group, and intermediate among patients in the Abciximab low dose heparin group. This suggests that regardless of the heparin regimen, the level of anticoagulation at the time of sheath removal is a major predictor of bleeding.

Table 40 Patients With Sheath **Site Bleeding By Level Of Anticoagulation At Time Of Sheath Removal**

Treated Patients	Total (n = 2173)	Placebo (n = 923)	**ReoPro Lo** Dose (n = 923)	**ReoPro Std** Dose **(n = 906)**
ACT ≤ 175 or **PTT ≤ 50** 'Patients **w/** prolonged bleeding, hematoma **> 5** cm, or **RP** Bleed	2173 117 5.4 **%**	717 26 3.6 %	743 3 9 5.2%	713 52 7.3 %
ACT > 175 or **PTT >** 50 Patients **w/** prolonged bleeding, **hematoma > 5 cm, or RP Bleed**	74 **11** 14.9 **%**	28 **1** **3.6 %**	**15** 2i.o %	31 **7** **22.6** %
Patients not evaluated	505 44 8.7 %	**178** 10 5.6 %	165 **13** I **7.9 %**	162 **21** 13.0 %

There were more patients in the placebo and Abciximab-standard dose heparin arms who received heparin for mom than 24 hours after the end of the index procedure. A greater percentage of the patients so treated had major bleeds than did patients treated with a shorter infusion (Table 41).

Table 41 Major Bleeding by Heparin Duration After Index Procedure

	Placebo (n = 939)	**ReoPro Lo Dose (n = 935)**	**ReoPro Std Dose (n = 918)**
Patients with intervention attempted	**923**	**923**	**906**
Patients receiving heparin after procedure	**294**	**249**	**225**
< 12 hour infusion **Patients w/** major bleeds **%**	**90** **2** **2.2 %**	**86** **2** **2.3 %**	**77** **6** **7.8 %**
12 - 24 hour infusion **Patients w/ major bleeds** **%**	**160** **1** **0.6 %**	**138** **3** **2.2 %**	**127** **0** **0 %**
> 24 hour infusion **Patients w/ major bleeds** **%**	**12** **1** **8.3 %**	**1** **0** **0 %**	**20** **0** **0 %**
Unknown duration **Patients w/ major bleeds** **%**	**32** **2** **6.3 %**	**24** **1** **4.2 %**	**19** **0** **0 %**

2. Major Bleeds in Patients With Bleeding History
No difference was observed in rates of major non-CABG bleeds in patients with and without a prior history of significant bleeding in this trial.

Reviewer Note: the rate of bleeding in patients in the EPIC trial who had a prior history of bleeding was significantly increased over that ofpatients without a prior bleeding history.

The ReoPro + Standard Dose Heparin arm showed the greatest number of bleeds in both patients with and without a history of bleeding, though there was no significant difference among treatment arms.

3. Bleeding By Heparin Administration
The protocol recommended, but did not require, that heparin be stopped at the end of the index intervention. This was done for 1,458 of the 2,572 patients who had an index intervention. Rates of major bleeding were low in these patients, 0.2 % in the placebo arm, and 0.6 % in the Abciximab Low Dose Heparin arm, and 1.6 % in the Abciximab Standard Dose Heparin arm.

Of the other patients in the study, the highest major bleeding rates were observed in those that had heparin continued after the procedure and restarted after femoral sheath removal. The number of patients in this group was smaller in all treatment arms, but the rates were substantially higher (2.4 to 6.3 %). This suggests a correlation between extent of heparin treatment and major bleeding in all treatment arms (Table 42).

Table 42 Major Bleeding by Heparin Duration

Patients with Major Bleeding	Placebo (n = 939)	ReoPro Lo Dose (n = 935)	ReoPro Std Dose (n = 918)
Patients w/ Heparin Stopped at End of Procedure	462 1 0.2 %	498 3 0.6 %	498 8 1.6 %
Patients w/ Heparin Stopped at End of procedure, Restarted after Sheath Removal	166 3 1.8 %	172 1 0.6 %	182 3 1.6 %
Patients w/ Heparin Continued until Sheath Removal	191 2 1.0 %	169 1 0.6 %	142 4 2.8 %
Patients w/ Heparin Continued after procedure and after sheath removal	103 11 4.2 %	80 5 6.3 %	82 2 2.4 %

4. **Investigator Reported Bleeding**
Investigator-reported bleeding was recorded for the time between randomization and discharge (or 7 days post randomization). Over half the patients in each treatment arm had Investigator reported bleeding; more in the ReoPro arms than in the placebo (heparin only) arm.

A small number had serious consequences; there were, however, no statistically significant differences between the ReoPro arms and the placebo arm (Table 43). There were 2 deaths reported due to bleeding in the ReoPro plus Lo Dose and ReoPro Standard dose arms (both due to ICH in the ReoPro Standard Dose Heparin arm, 1 due to ICH in the ReoPro Lo Dose Heparin arm, and 1 due to bleeding complications of cardiac surgery in the ReoPro Low Dose Heparin arm), and none in the placebo arm. There were an equal number of patients with serious hypotension in the placebo and the Reo Pro Standard dose heparin arms (5 each) but only 2 in the ReoPro low dose heparin arm. There were 12 patients with other serious adverse events related to bleeding in the ReoPro Standard dose arm, while the ReoPro low dose heparin arm had none.

Table 43 Investigator Reported Bleeding

	Placebo n=939	ReoPro Low Dose n=935	ReoPro Std Dose n=918
Patients with Investigator Reported Bleeding	420 (44.7)	529 (56.6)	574 (62.5)
Deaths due to bleeding	0	2	2
Other serious AE due to bleeding	5	0	12
Serious Hypotension due to bleed	5	2	5

Reviewer Note: The higher rates of bleeding in the ReoPro Standard Dose Heparin arm strongly suggests the we of the combination of Abciximab and Standard dose heparin is not desirable.

VII. Interim Analysis Results

A decision was made by the SEMC to stop the trial after the Interim Analysis of results on the first 1500 patients due to strikingly positive efficacy findings in the ReoPro treated patients compared to placebo, with the best findings in the low dose heparin arm (see table 44). The primary endpoint of this analysis was death and MI at 30 days.

Table 44a Interim Analysis – Death And MI At 30 Days

Patients w events	Total n = 1500	Placebo n = 492	Reo Lo Hep n = 510	Reo Std Dose n = 498
Finalized Analysis				
n	75	42	15	18
%	5.1 %	8.6 %	3.0 %	3.7 %
p value*			.00006	< .00001

* Logrank Test, Sig < .05

Reviewer** Note: **SEMC communications** have **been reviewed.** **It appears the integrity** of **the data was not compromised in the process, and that procedures were followed as outlined in the protocol and analytic plan** for **the study.

Note that according to the Analytic Plan, if the trial was stopped early for efficacy, the composite of death and MI at 30 days became the primary endpoint for the trial, superseding the prespecified primary composites which included urgent revascularizations at 30 days and repreat revascularizations at 6 months. Table 44b presents the endpoint of death and MI at 30 days for all 2,792 patients.

Table 44b Final Analysis -- Death And MI At 30 Days

Patients w events	Placebo n = 939	Reo Lo Hep n = 935	Reo Std Dose n = 91
n %	85 9.1 %	35 3.8 %	38 4.2%
p value*		< .0001	< .0001

* 1 sided Logrank Test, Sig < .05

VIII. Primary STENT Substudy

Initially, patients who were to be receiving STENT placement as primary treatment for coronary artery stenosis were excluded from participation in the EPILOG study. Due to the growing use of primary intracoronary STENTing, a substudy was incorporated into the larger trial to evaluate the concurrent use of Abciximab and STENTS with a protocol amendment in June 1995. A total of 123 patients were enrolled into the primary STENT substudy at 22 centers between August and December 1995.

Patients who were deemed suitable candidates for either STENT implantation or primary angioplasty for treatment of the target vessel were randomized into this substudy. Patients were randomized either to treatment with PTCA or primary STENT placement, and then to treatment with one of the 3 main treatment arms of the overall EPILOG study.

Of the 123 patient in the substudy, 65 were randomized to PTCA and 58 to primary treatment with a STENT. The distribution of patients was even across the 3 treatment arms of the main trial (see Table 45). Only 1 patient in the substudy was not treated with study agent; that patient was in the Abciximab Low Dose Heparin arm and randomized to PTCA. Unblinding of study agent or heparin occurred in only 2 patients in the substudy, one each in the PTCA and STENT arms. The PTCA and STENT groups were well matched on all demographic characteristics (see table 46).

Table 45 Distribution of Patients in Primary STENT Substudy

	Placebo + Std Hep	Abciximab + Lo Hep	Abciximab + Std Hep
PTCA	20	24	21
STENT	20	20	18

'able 46 Demographics of Patients in STENT Substudy

	PTCA (n = 65)	STENT (n = 58)
Male	50 (77 %)	44 (76 %)
Median Age (yrs)	61.5	61.1
Median Weight (kg)	65	58
Caucasian	57 (88 %)	52 (90 %)

Indications and Risk Status: The most common indication for the index intervention in substudy patients was unstable angina (42 %). Patients with recent MI comprised 25 % and patients with positive functional tests 23 %. These were similar to the proportions in the main study. Sixty-three percent of patients randomized to PTCA in the substudy were designated as high risk at randomization, as were 75 % of the patients randomized to STENT placement.

Concomitant Treatment: Heparin administration and ACT values during the procedure were generally similar to those of the overall study population. Post procedure heparin use was less common in substudy patients (15 % vs 28 % in the main study) in each of the 3 treatment groups. Ticlopidine was also administered to over 70 % of the patients randomized to STENT, and to 21 % of the patients randomized to PTCA in the substudy.

Treatment Received: STENTs were allowed for "bailout" of patients treated with PTCA. Of the 65 patients randomized to PTCA, 50 (77 %) had PTCA only, 14 (21 %) received at least one STENT, and 1 had failure to cross the lesion. Of the 58 patients randomized to STENT, 1 had PTCA only and 1 did not have treatment &tempted.

Procedure Characteristics: The median duration of the index procedure was longer for STENT patients (40.5 minutes compared to 24.5 minutes for PTCA patients). The procedure was successful by angiographic outcome criteria for all lesions attempted in 93 to 95% of PTCA patients, and 97 to 100 % among patients randomized to STENT.

Primary Endpoint Events: The same primary endpoints were evaluated as in the main study. The Abciximab patients are combined for this analysis. Event rates at 30 days were lower with Abciximab than placebo for both PTCA and STENT patients (see Table 47), and at 6 months for PTCA patients but not for STENT patients. STENT patients fared better than PTCA patients in the placebo arm at both 30 days and 6 months; and STENT patients treated with Abciximab did slightly better than similarly treated PTCA patients at 30 days, but not at 6 months.

Table 47 Primary Endpoint Event Rates in PTCA or STENT Patients

	Placebo + Std Hep PTCA n = 20	Abciximab + Hep PTCA n = 45	Placebo + std Hep STENT n = 20	Abciximab + Hep STENT n = 38
Death, MI or urgent revasc at 30 days	5 (25.0)	4 (8.9)	3 (15.0)	3 (7.9)
Death, MI, or repeat revasc at 6 months	10 (50.0)	11 (24.0)	4 (20.0)	11 (28.9)

Secondary Endpoint Events: Event rates were assessed for combined placebo and Abciximab groups. Fewer patients randomized to STENT had repeat revascularization at 30 days (composite 18.5 % PTCA patients and 10.3 % STENT patients). The composite including target vessel revascularization at 6 months was less common among patients randomized to STENT (32 % PTCA and 22 % STENT patients). The percentage of patients with a composite including death, MI, repeat revascularization or clinically significant angina (a novel endpoint combination in this substudy) was somewhat better among STENT patients (36 % PTCA and 31 % STENT patients).

Safety Results: Major bleeding occurred in 4.6 % of patients randomized to PTCA and 5.2 % of patients randomized to STENT. All major bleeds among STENT patients were related to sheath site bleeding, whereas all major bleeding events in PTCA patients were related to CABG. Minor bleeding occurred more frequently in STENT patients (62 % vs 1.7 % of PTCA patients). Transfusions of PRBCs were given more often to PTCA patients (7.7 %) than to STENT patients (52 %).

Reviewer Comments on the STENT Substudy:

Efficacy--the 30 day composite endpoint results favor the use of Abciximab in both patients undergoing PTCA and primary STENT placement. The factors responsible for the relatively poorer 6 month outcomes in STENT patients are not clear. It is difficult to draw conclusions regarding the efficacy of Abciximab in the setting of primary STENT placement due to the small numbers of patients treated in the substudy.

Safety--The occurrence of major bleeds in the STENT patients at the sheath site and higher rate of minor bleeds in the STENT patients may be explained by the treatment of the STEW patients wtth other antithrombotic agents, namely Ticlopidine, in addition to the heparin, aspirin, and Abcfximab. This is consistent with the findings of the main study and of other studies that the risk of bleeding is increased in patients receiving multiple antithrombotic, antiplatelet, and/or thrombolytic agents concomitantly.

This study does not adequately assess either the risks or benefits of Abciximab treatment in conjunction with STENT placement.

IX. REVIEWER COMMENTS AND CONCLUSIONS

A. STUDY MANAGEMENT

1. The composition and performance of the CECs in reviewing endpoint events, and SEMC at interim and final analyses appear reasonable. The decisions and the integrity of data assessment procedures appear reasonably conducted as well.

B. STUDY CONDUCT

1. Randomization -the integrity of the randomization procedure to allocate patients to arms of the study appears reasonable. At issue is the scheme for allocation of patients enrolled to risk categories. Identifying patients prospectively (at randomization) by the likelihood of ischemic events should be the more clinically relevant assessment, However, the risk status of such a significant portion of the patients was changed at the time of CRF completion, that it casts doubt on the validity of the randomization categorization. The categorization performed at the time of CRF completion was subject to bias in that the ratings were done after the procedure had b&n completed and the lesion more extensively visualized, and in some cases, after the post-procedure hospital course was known. A mom detailed and formalized assessment procedure was used, and thus the categorization procedure at the time of CRF completion may have favored more rankings in the high risk category. The Agency has requested that the sponsor perform an independent assessment of a sample of the pre-procedure angiograms in an attempt to validate the risk status assessment performed at randomization. The sponsor contends that a ze-review will be likely to yield results differing from either the randomization or the CRF assessment, and that the ACC/AHA lesion classification system is not reliable enough to be used prospectively to categorize lesions with clinical relevance. The results of the angiogram re-review are pending at the time of completion of this review.

2. Blinding appears to have been reliably maintained in all treatment arms. The relatively small number of instances of unblinding do not appear to have compromised the integrity of the study.

3. Completeness of follow-up is good. There are a small number of missing values that have not impacted the results of the study.

C. EFFICACY FINDINGS

1. Success has been demonstrated on the 30 day primary composite endpoint, and the benefit appears sustained at 6 months It does appear that the agent can prevent cardiac ischemic complications secondary to coronary artery thrombus. These data confirm the results of the EPIC trial for patients at high risk. The claim for the extension of benefit to patients not deemed at such high risk cannot be determined from the data presented (see # 4).

2. Most of the benefit appears to be in prevention of myocardial infarction, most of which are large non Q wave MIs. There is also a trend toward reduction of Q wave MI, though the numbers of these events are smaller. There are fewer deaths in the ReoPro treated arms, but the numbers are too small to draw conclusions.

3. The 6 month primary endpoint shows benefit in the ReoPro arms by the sponsor's analysis using the logrank test on-time to event data, although the magnitude is less than the benefit seen on the 30 day endpoint. When the proportion of patients with endpoint events at 6 months is compared using the Fisher exact test, there is no clear advantage seen in the Abciximab treatment arms,

The number of total revascularization procedures is not reduced in ReoPro treated patients at 6 months, particularly among high risk patients. This suggests that Abciximab does not retard the underlying atherosclerotic disease process in either the treated vessel or other coronary vessels. Results of the Angiographic Substudy will be reviewed separately.

4 Claim of Efficacy for Low and High Risk Subgroups -- Many of the patients who were initially determined to be of low risk status subsequently were reclassified as higher risk at the time of CRF completion, undermining the validity of the initial risk status assessment.

It is not clear which, if either, risk assessment represents a clinically reliable classification of the patients who arc candidates for percutaneous coronary intervention. Examination of the primary endpoint confirms the efficacy of Abciximab in patients at high risk of ischemic cardiac events regardless of which classification is used. The as-randomized scheme also demonstrates efficacy in the low risk subset. The per-CRF results fail to support efficacy in the low risk subset, however.

Comment:

5. Efficacy across procedures other than balloon angioplasty is not as clearly established. There were few patients in the study with other procedures. However, the trends for those patients appear to be in the same direction.

D. SAFETY FINDINGS

1. Substantial improvement in bleeding rates was seen in all arms over that seen *in* EPIC trial Weight adjustment of heparin, and the reduced duration and reduced dosage of heparin were the most important factors in reducing bleeding. Adherence to stricter anticoagulation guidelines and more stringent access site management appears to have significantly contributed to lowering the bleeding in all treatment arms compared to that seen in EPIC. Early sheath removal itself did not contribute much to the reduced bleeding, but discontinuation of heparin in order to get the ACT down prior to sheath removal was key.

2. There was no association of increased bleeding with lower body weight or gender, as seen in the EPIC trial.

3. Most bleeds occurred at the femoral arterial sheath site. There were more non-sheath site bleeds among patients' in the Standard Dose heparin arms than in the Low Dose heparin arm.

4. The near double rate of minor bleeding (still a significant blood loss) in the ReoPro Standard Dose heparin rum, as well as the 2 cases of ICH in that arm, provide evidence that the ReoPro Standard dose heparin regimen is not a desirable combination.

6. The number of ICH is small overall, but the data suggest some additional risk may be introduced when ReoPro is added to heparin, either in standard or low doses.

7. The use of low dose weight adjusted heparin in combination with ReoPro appears to have the strongest safety profile of the 3 regimens compared.

X. RECOMMENDATIONS

A. Indication and Claims

1. Extension of benefit to patients not deemed at high risk of abrupt closure of the treated coronary artery rests on the resolution of the risk status assessment issue. At this time the supplement is not approvable for this extended patient population. Additional information has been requested from the sponsor to determine the reliability of the risk classification scheme used at randomization.

2. The study strongly supports the recommendation of the combination of weight adjusted heparin and reduced dosage and duration of heparin as concomitant therapy, along with adherence to stricter anticoagulation guidelines and more stringent arterial access site management, as means to reduce bleeding complications.

B. Labelling Comments .

1. The safety data from the Abciximab low dose heparin regimen should be incorporated into labelling as soon as possible.

2. While the efficacy data from the EPILOG trial appear to indicate a benefit among the patients enrolled into the trial, the risk status of these patients is still under review. Efficacy data will not be included in the label at this time, until the risk status assessment issue can be resolved and the study results interpreted.

3. The sponsor presents data on intracranial bleed in aggregate from all trials completed to date. These data have been verified as supported by all 3 trials, and presentation of the aggregate statistic is appropriate.

4. The proposed -label submitted by the sponsor also includes changes related to other studies. Comments are as follows:

   a) Extrapolation of the data from EPILOG on reduced bleeding to the unstable angina indication appears warranted, and the sponsor's recommendation that the lower anticoagulation target be adhered to during the PTCA for unstable angina patients receiving the 18 to 24 hour regimen is appropriate.

   b) The readministration study data will be discussed separately in that review.

   c) The EPIC data on _____ and the clinical pharmacology claims regarding the vitronectin receptor will be reviewed separately in BLA # 97-0201.

Appendix 1

CHARACTERISTICS OF TYPE A, B, AND C LESIONS

Type A lesions **(minimally complex)**
- Discrete **(length** < 10 mm)
- **Concentric**
- Readily accessible
- **Nonangulated segment** (< 45°)
- **Smooth contour**
- **Little or no calcification**
- **Less** than **totally occlusive**
- Not **ostial in** location
- No major side branch **involvement**
- Absence of **thrombus**

Type B lesions **(moderately complex)**
- Tubular (length **10** to 20 mm)
- **Eccentric**
- Moderate **tortuosity** of proximal segment
- Moderately **angulated segment** (> 45°, < 90°)
- **Irregular contour**
- Moderate or **heavy calcification**
- Total occlusions < 3 mo old
- **Ostial** in location
- **Bifurcation** lesions **requiring** double **guidewires**
- **Some thrombus** present

Type C **lesions** (severely **complex)**
- **Diffuse** (length > 2 au)
- **Excessive tortuosity of proximal** segment
- Extremely **angulated** segments > 90°
- Total occlusions > 3 mo **old and/or bridging collaterals**
- **Inability** to protect **major** side **branches**
- **Degenerated** vein grafts with friable **lesions** ,

(From: Ryan et **al. Guidelines** for **Percutaneous Translumin** al **Coronary** Angioplasty: A Report **of the American** College of **Cardiology/American Heart Association Task** Force on Assessment of **Diagnostic** and **Therapeutic Cardiovascular Procedures (Committee** on Per **cutaneous Transluminal Coronary Angioplasty).** J **Am Coll Cardiol** 1993; **2033-54.**

CRF Page

Appendix 2

CENTOCOR

Phase III c7E3 Fab
EPILOG Trial

CENTOCOR STUDY NO. CO1 16T16 -

PATIENT ENROLLMENT NO. ___ ___ ___

PATIENT INITIALS ___ ___ ___ (first mid last)

1

SEGMENT INFORMATION

Complete a **separate** page for each **lesion** undergoing trealment.

Segment #: _____

Procedure (by codes) In order used:

___ ___ ___ ___ ___ ___

1 = PTCA 2 = DCA 3 = TEC Alhereclomy 4 = Laser 5 = Rotational Atherectomy
6 = Stent implantation 7 = Olher FDA approved device, specify: _____

Primary Target Lesion7 ☐1 Yes ☐2 No

Was lhis **lesion** subject to previous percutaneous Intervention?
☐1 Yes ☐2 No ☐3 Unknown

PRE-INTERVENTION

TIMI Grade: _____ % Slenosls: _____

Check one column (lesion type) for each characterlslk **listed** below.

	Type A	Type B	Type C
Length	01 <10 nun	02 10-20 mm	☐3 > 20 mm
Eccentricity	☐1 Concentric	☐2 Eccentric	
Accessibility	☐1 Readily Accessible	☐2 Moderate tortuosity of proximal segment	☐3 Excessive tortuosity of proximal segment
Lesion Angulation	☐1 < 45°	☐2 > 45° and < 90°	☐3 > 90°
Lesion Contour	☐1 Smooth	☐2 Irregular	
Ostial	☐1 Not ostial	☐2 Ostial	
Calcification	☐1 Little or none	☐2 Moderate to heavy	
Thrombus	☐1 Absent	☐2 Present	
Occlusion	☐1 Less than total	☐2 Total< 3 months old	☐3 Total > 3 monlhs old
Bifurcation	☐1 No major involvement	☐2 Bifurcation lesions requiring dbl guide wires	☐3 Inability to protect major side branches
Grafts	☐1 NA		☐3 Degenerated vein grafts with friable lesion

INTERVENTION OUTCOME

Final **TIMI** Grade: _____ Final % Stenosls: _____

If % Stenosis **> 50%,** check reason(s) for fallure: ☐1 Failure to cross
☐2 Faifure to dilate
☐3 Abrupt closure
☐4 Dissection
Os Other: _____

Stent(s): ☐1 Yes, specify time: ___ ___ (24 hr clock)
0-2 No

If Yes: Type (See code list) Size

_____ ___ mm
_____ ___ mm
_____ ___ mm

Codes for Types of Stents
1 = Palmaz Schatz
2 = Gianturco-Roubin
3 = Wiktor
4 = Other, specify on line

Was the patient referred for urgent CABG for a complication **in** treating **this** segmenl? ☐1 Yes 02 No

Dissection: ☐1 None ☐2 Minor ☐3 Major
if present: ☐1 Transverse ☐2 Longitudinal ☐3 Spiral

Perforation (angiographic evidence of **true** vascular **perforation):**
☐1 **None** ☐2 **Localized** ☐3 Tamponade

Thrombus/Filling Defect (Check ail that apply):
Ci None 0 Haziness 0 Discrete Defect ☐ **Contrast** Staining

Distal Emboiization: ☐1 None ☐2 Present

Temporary Coronary Occlusion? ☐2 None ☐1 Present
if present: **Minimum TIMI** grade: _____

Side Branch Occlusion (check one):
☐1 None ☐2 Small ☐3 Medium ☐4 Large ☐5 Not Applicable

Other interventions (Check all that **apply):**
0 **Perfusion catheter** 0 Olher: _____
0 **IABP** 0 None
0 Jhrombolytks

phc 10-MAR-1995

Investigator's Signature: _____ **Date:** - - - - - -19___ (D-M-Y)

1/2

Appendix 3

PILOG

ENROLLMENT FORM

Site# C0116T16
Patients Initials
Study Number
Kit #

TO RANDOMIZE A PATIENT: CALL 1-800-545-DUKE (3853)
Do not call earlier than 2 hours prior to index intervention

Date of enrollment ____/____/____ (dd-mon-yr)
Date of birth ____/____/____ (dd-mon-yr)

Enrollment time ____:____ (24-hr clock)
Weight ____ kg
Is the patient a diabetic ? YES or NO
Gender: Male or Female

History of MI YES or NO
if yes...Has the most recent MI occurred within 7 days? YES or NO
if yes...Is index intervention on the IRA? YES Or NO

Please obtain written informed consent and complete the following **information** PRIOR **to calling for Randomization**

This Patient:	TRUE	FALSE
1.) is at least 21 years old and, if a woman of child-bearing potential, has been made explicitly aware that c7E3 Fab may cause excessive menstrual bleeding and increased risk Of uterine bleeding which could affect implantation of an ovum or cause abortion	☐	☐
2.) is referred for elective or urgent percutaneous coronary intervention with an FDA approved device	☐	☐
3.) has a target artery (native or graft) stenosis of ≥ 60% (visual estimation)	☐	☐
4.) has provided written informed consent before enrollment and has agreed to comply with all protocol-specified proccdurcs	c l	☐
5.) has NOT dad unstable angina/non Q wave myocardial infarction meeting EPIC criteria within the previous 24 hours	☐	☐
6.) has NOT had acute Q-wave myocardial infarction meeting EPIC criteria with onset of chest pain within the previous 24 hours	☐	☐
7.) does NOT have active internal bleeding, a history of hemorrhagic diathcsis	☐	☐
8.) has NOT had major surgery or serious trauma within 6 weeks before study enrollment	☐	☐
9.) has NOT had GI or GU bleeding of clinical significance within 6 weeks before enrollment	☐	☐
10.) has NOT had a CVA within 2 yrs. before enrollment, or any CVA with residual neurological deficit	☐	☐
11.) does NOT have intracranial neoplasm, arteriovenous malformation or aneurysm	☐	☐
12.) has NOT had puncture of noncompressible vessel within 24 hrs prior to enrollment	☐	☐
13.) does NOT have confirmed HTN with SBP>180mmHg or DBP >100mmHg	☐	☐
14.) is NOT receiving oral anticoagulants (eg. warfarin) at time of enrollment	☐	☐
15.) does NOT have baseline PT measurement >1.2 times control in the absence of heparin therapy	☐	☐
16.) either does NOT have a >50% stenosis in the left main artery or, if > 50% occluded the left coronary system is protected with at least one patent bypass graft	☐	☐
17.) is NOT scheduled for rotational atherectomy	☐	☐
18.) is NOT scheduled for stent implantation in a patient not suitable for enrollment into the Primary Stent Substudy	☐	☐
19.) has NOT had percutaneous coronary intervention within the previous 3 months	☐	☐
20.) does NOT have a presumed or documented history of vasculitis	☐	☐
2 1.) does NOT have a known allergy to 7E3 or other murine proteins	☐	☐
22.) does NOT have known allergy or intolerance to aspirin	☐	☐
23.) has NOT participated in other clinical research studies involving the evaluation of other investigational drugs or devices within 7 days of enrollment	☐	☐

Specify most severe coronary artery morphological characteristics at the time of randomization in any artery to bc treated during the index intervention (ACC/AHA criteria):

____ One type B ≥ Two type B ____ ≥One type C ____ None of the above

Do you plan to enroll this patient in the stent substudy ☐ ☐

COMPLETE FOR ANGIOGRAPHIC SUBSTUDY PATIENTS ONLY:
Specify Primary Target Lesion:_____ (Usc lesion segment code from back of this form)